MS:air mixture.

- Mohr and Reznik (1978): Hyperplasia and metaplasia observed in the trachea and bronchi of mice exposed to MS via inhalation.

- Dalbey *et al.* (1980): Respiratory tumors observed in MS-exposed Fischer-344 rats.

OSHA cited three other studies but the.references were either incomplete (Ref. 247: Otto and Elmenhorst; Ref. 197: Leuchtenberger and Leuchtenberger) or not given at all (Ref. 327).

- Leuchtenberger and Leuchtenberger (?): Pulmonary adenomas and adenocarcinomas were induced in Snell's mice by the gas phase but not by the whole smoke in mice exposed to whole MS.

- Otto and Elmenhorst (?): OSHA noted that these investigators "have shown that there are carcinogenic constituents in the vapor phase of tobacco smoke... The particulate matter was removed by passing the smoke through a Cambridge filter."

- Ref. 327 (not given): OSHA noted that in this study, hyperplasia and metaplasia were observed in the trachea and bronchi of mice exposed to MS via inhalation.

In its comments on the only two bonafide ETS inhalation studies (Coggins *et al.*, 1992, 1993) discussed in its report, OSHA (OSHA, 1994: page 15980) stated:

> Male and female Sprague-Dawley rats exposed nose only to ETS developed nasal hyperplasia; this condition was reversible. No effects in the lung were observed.

and then proceeded to criticize the studies in the following language:

> Rats are obligatory nose-breathers, and the anatomy and physiology of the respiratory tract and the biochemistry of the lung differ between rodents and humans. Because of these distinctions, laboratory animals are likely to have different deposition and exposure patterns for the various cigarette components in the respiratory system. For example, rodents have extensive and complex nasal turbinates where significant particle deposition could occur, decreasing exposure to the lung. These anatomical and physiological differences, aside from the subchronic exposure, may partially account for absence of any lung tumors in the study by Coggins *et al.* [*sic*]

It would appear from these statements that OSHA attributes the failure of Coggins *et al.* (1992, 1993) and others to produce tumors in rodents exposed "nose-only" to MS or ETS to the following factors: (1) the complex nasal turbinate process in the rodent and (2) the exposure level. If, during "nose-only" exposure to MS, the nasal turbinate process prevents MS from reaching the lungs, it apparently does not do so when rodents are exposed to Diesel exhaust aerosol. Mauderly *et al.* (1987) reported the production of squamous cell carcinoma in rodents exposed to Diesel engine exhaust in a procedure similar to that used with tobacco smoke.

OSHA either inadvertently or deliberately omitted any comment on the known effectiveness of recent "nose-only" exposure systems in delivering substantial amounts of the administered tobacco smoke to the target organ, the lung.

When the "whole-body" procedure of exposure of laboratory animals to tobacco smoke was found to be inadequate, "nose-only" exposure systems were explored and eventually several acceptable systems were developed. Radiolabeled or "indicator" compounds were used to determine whether the administered tobacco smoke indeed reached the lungs of the exposed animal. The degree of deposition in the lungs of laboratory animals exposed to MS via "nose-only" inhalation has been measured in tobacco smoke exposure systems such as that used by Coggins *et al.* (*cf.* Henry and Kouri, 1984 and Microbiological Associates, 1984 and references therein). Deposition of TPM in the lung was 72%. However, BaP and nicotine were extensively and rapidly redistributed after the smoke exposure. For nicotine originally deposited in the lungs, 17% and 78% were redistributed to the head and other internal tissues, respectively; for BaP deposited in the lungs, 13% and 45% were redistributed to the head and other internal tissues, respectively.

One might ask the question of why OSHA is so critical in its report of the only two studies it cited that dealt with ETS exposure. Is it because the studies were conducted by tobacco industry research personnel, Coggins *et al.* from R. J. Reynolds Tobacco Company R&D?

It is also interesting that OSHA was so selective in its choice of tobacco smoke inhalation studies to discuss. It failed to cite numerous other inhalation studies conducted over the past six decades, some relatively recently, in which no squamous cell carcinomas were reported in animals exposed to tobacco smoke via inhalation, *e.g.*, the studies by Campbell (1936), Mertens (1941), Lorenz *et al.* (1943), Essenberg (1952, 1954b), Passey *et al.* (1954), Essenberg *et al.* (1955, 1956), Mühlbock (1955), Lupu and Veliçan (1957), Komczynski (1958), Leuchtenberger *et al.* (1958, 1960a, 1960b), Passey (1958), Peacock (1958), Guerin (1959), Dontenwill and Mohr (1962), Leuchtenberger and Leuchtenberger (1962), LeBouffant *et al.* (1980), Wehner *et al.* (1981), Motulionis (1984), Henry and Kouri (1984, 1986), and Wilbourn *et al.* (1986). OSHA also did not include the comments of IARC (1986) on the repeated failure of experimentalists to induce squamous cell carcinoma in laboratory animals exposed via inhalation to tobacco smoke.

Another example of OSHA's attempt to present the results from a particular piece of research to bolster its position on ETS is its discussion of lung cancer in pet dogs (OSHA, 1994: page 15981). Even though it concedes, at the very end of the discussion that the result was statistically insignificant, OSHA dwelt at length on a comparison of the incidence of lung cancer in pet dogs exposed to their owners' smoke *vs* that in pet dogs whose owners did not smoke:

> Environmental tobacco smoke induced carcinogenicity is also supported by a case-control study of lung cancer in pet dogs [Reif *et al.*, 1992].The study compared the incidence of lung cancer in pet dogs exposed to their owners' smoking versus dogs whose owners did not smoke. There was an elevated risk of lung cancer (Relative Risk = 1.6) observed in pets with smoking owners. *However, the analysis was insignificant, perhaps in part due to small sample size.* (*Emphasis added*: AR)

The incidence of lung cancer not only in pet dogs but also in specimens in zoological gardens was studied in detail some years ago when it was fashionable to indict urban air

pollution not ETS as the responsible factor. When these studies were conducted, the analogy was drawn between humans residing in industrial or urban areas and the zoological specimens housed in zoological gardens in urban areas. In many of the studies, the sample size was *not* small.

Lombard and Witte (1959) in their study of specimens at the Philadelphia Zoological Gardens reported the following:

- The frequency of malignant tumors increased during the period 1935 to 1955 vs 1901-1934 in the orders *primates*, *carnivora*, and *artiodactyla* but decreased in the orders *rodentia* and *marsupalia*; benign tumors increased in all orders but *rodentia*.
- In 1935, the nutrition of the diet supplied the zoological specimens was significantly improved.
- Four orders of birds showed increases in both benign and malignant tumors between the two periods specified.
- The order *anseriformes* (goose) showed a high incidence of lung tumors in the period 1945-1955. This finding was attributed to the fact that these specimens were maintained in outdoor pens all year long, thus were exposed continuously to urban air pollution. Additional lung tumors were observed from 1955 to 1960.

The authors attributed the increased incidence of tumors in the specimens to two factors: environment and nutrition.

In their study of 9,781 dogs autopsied between 1924 and 1954, Ten Thije and Ressing (1956) found 22 cases of lung cancer, 16 between 1951 and 1954. Since the canine lung tumor is quite large, their opinion was that the increased lung cancer incidence was not attributable to improved diagnosis. Increased lung cancer incidence in dogs was also reported by Krahnert (1953).

At necropsy, Catcott *et al.* (1958) examined 51 dogs from two areas of Los Angeles County with contrasting air pollution patterns. No pathological differences were observed in the tracheobronchial trees of the two groups.

Cohen (1965) observed 44 dogs with lung tumors among 60,000 dogs (56% male, 44% female) examined over a 12-year period. Very few of the dogs lived in urban areas. Comparison of the first 5-year period with the last gave 15 *vs* 24 lung tumor-bearing dogs, respectively. The average age of the dogs with lung tumors was 9.1 year *vs* 4.0 year for the total sample. Cohen attributed the increased incidence of canine lung cancer to increase in life span and improved diagnosis during the preceding 20 years. Nielsen (1965) examined 9,263 Ohio dogs and 4,616 Connecticut dogs and reported the following:

| State | Environment | Period | Number | Number with Lung Tumors |
|---|---|---|---|---|
| Ohio | rural & urban mix | 1928-1949 | 9,263 | 0 |
| | | 1950-1954 | | 3 |
| | | 1955-1959 | | 11 |
| Connecticut | rural | 1961-1964 | 4,616 | 11 |

Nielsen attributed the increased incidence of lung cancer in his sample to increased longevity (the average life span, depending on the breed, had increased from 4 to 7 years during the preceding 20 years) and improved diagnosis during the preceding 25 years. The attempt to relate the difference in lung cancer incidence to air pollution gave inconclusive results.

### *Studies with Individual Cigarette Smoke Components*

Aviado (1990) summarized the data reviewed by RTECS (Registry of Toxic Effects of Chemical Substances) (1987) on the production of lung tumors in laboratory animals treated via various routes with PAHs and heterocyclic compounds listed by Hoffmann and Hecht (1990) as MS tumorigens. The information reviewed by RTECS and summarized by Aviado is shown in **Table 17**. RTECS rated most lung cancer production data as ''equivocal,'' yielding ''uncertain but seemingly positive results.'' The only positive results not rated ''equivocal'' by RTECS were those obtained in experiments where the test compound was administered by intrathoracic implantation (I/Th) or by intratracheal injection (I/Tr). Inhalation studies, the only studies really relevant to the possible role of ETS in lung cancer in nonsmokers, were all rated ''equivocal.'' The inhalation studies rated by RTECS involved BaP exposure.

The evidence available to date on the tumorigenicity of PAHs to the pulmonary system of laboratory animals exposed via the inhalation route is nonexistent for several of the PAHs listed by Hoffmann and Hecht (1990) as MS tumorigens or is categorized as ''equivocal'' by RTECS for those PAHs on the list that have been tested via the inhalation route.

It has been known for over five decades (Shear and Leiter, 1941) that it is not appropriate to extrapolate the biological effect obtained by administration of a PAH via one route to that anticipated for administration by another route. The tumorigenicity via inhalation of a PAH to the pulmonary system cannot be predicted from its tumorigenicity observed in skin-painting studies or in subcutaneous-injection studies. The lack of validity of such an extrapolation is well-documented in numerous studies involving the tumorigenicity of PAHs administered via different routes. As Shimkin (1955) wrote:

> The investigations of Andervont and Shimkin [1940]...showed that there was no complete parallelism between the ability of some compounds to produce pulmonary tumors in strain A mice and their carcinogenicity as revealed by the induction of sarcomas following subcutaneous injection or of carcinomas following percutaneous application. Badger *et al*....and Kennaway *et al*.... pointed out a number of polycyclic hydrocarbons that were of low but positive carcinogenic potency in producing cutaneous carcinomas in mice and were inactive in eliciting sarcomas upon

**TABLE 17: PRODUCTION OF LUNG TUMORS IN LABORATORY ANIMALS TREATED WITH POLYCYCLIC AROMATIC HYDROCARBONS, WITH AZA-ARENES, OR WITH *N*-NITROSAMINES**

| | Administration Route | | | | | | |
|---|---|---|---|---|---|---|---|
| Compound | Oral | S/C | I/P | I/Th | I/Tr | I/V | Inh |
| *PAHs* | | | | | | | |
| benz[*a*]anthracene (BaA) | .. | .. | .. | .. | .. | m[a] | .. |
| benzo[*b*]fluoranthene | .. | .. | .. | r | .. | .. | .. |
| benzo[*j*]fluoranthene | .. | .. | .. | r | .. | .. | .. |
| benzo[*k*]fluoranthene | .. | .. | .. | r | .. | .. | .. |
| benzo[*a*]pyrene (BaP) | .. | r[a] | .. | r | hm | m[a] | hm |
| dibenz[*a,h*]anthracene (DBA) | r | r[a]m[a] | .. | m[a] | .. | m[a] | .. |
| dibenzo[*a,i*]pyrene | .. | m | .. | .. | h | .. | .. |
| indeno[1,2,3-*cd*]pyrene | .. | .. | .. | r | .. | .. | .. |
| *Aza-arenes* | | | | | | | |
| dibenz[*a,h*]acridine | .. | .. | .. | r | .. | m[a] | .. |
| *NNAs* | | | | | | | |
| *N*-nitrosodimethylamine (NDMA) | m | .. | .. | .. | h | .. | m |
| *N*-nitrosoethylmethylamine (NEMA) | mr | .. | .. | .. | .. | .. | .. |
| *N*-nitrosodiethylamine (NDEA) | .. | m | .. | .. | h | .. | h |
| *N*-nitrosopyrrolidine (NPYR) | m | m | h | .. | .. | .. | .. |
| *N*-nitrosodiethanolamine (NDELA) | .. | h | .. | .. | .. | .. | .. |
| *N'*-nitrosonornicotine (NNN) | .. | h | .. | .. | .. | .. | .. |

[a] Data from Shimkin (1955); all other data from Aviado (1990).

Abbreviations

| | | | |
|---|---|---|---|
| Oral | = oral administration | m | = mouse |
| S/C | = subcutaneous injection | h | = hamster |
| I/P | = intravenous injection | r | = rat |
| I/Th | = intrathoracic implant | .. | = no study considered |
| I/Tr | = intratracheal injection | | |
| I/V | = intravenous injection | | |
| Inh | = inhalation | | |

subcutaneous injection. By the same token, no exact parallelism or even the same qualitative response should be anticipated in results obtained by the pulmonary induction technique and in those obtained by the subcutaneous or percutaneous methods.

Some of the data to which Shimkin (1955) referred are incorporated into Table 17 for five of the compounds (BaA, BaP, DBA, dibenz[*a,h*]acridine, 7*H*-dibenzo[*c,g*]carbazole) listed by Hoffmann and Hecht (1990). No data have been generated to justify the extrapolation of skin-painting or subcutaneous-injection findings with these or similar PAHs and aza-arenes to a pulmonary situation.

Another class of MS components discussed at length by Aviado (1990) with regard to their tumorigenicity in the pulmonary system was the NNAs. **Table 17** also summarizes those studies discussed by Aviado in which lung neoplasms were observed in laboratory animals treated with an NNA by the administration route indicated. These data were reviewed by RTECS (1987) and the findings in the inhalation experiments with NNAs categorized as "equivocal."

Aviado (1990) noted that the NNA dose levels that resulted in lung tumor production whatever the administration route were substantially greater than the levels of NNAs detected in indoor air and attributed to ETS, *e.g.*, inhalation by mice of NDMA at a dose level of 200,000 $ng/m^3$ (200 $\mu g/m^3$) produced lung tumors but this dose level should be compared to the $ng/m^3$ level (10-240 $ng/m^3$) at which NDMA has been detected in ETS-containing air (Aviado, 1990). Aviado (1990) concluded:

> Based on these data, it is not 'biologically plausible' that nitrosamines in ETS contribute to pulmonary carcinogenesis.

Aviado (1988) discussed the carcinogenicity of five MS components also found in SS and tested for carcinogenicity in laboratory animals via inhalation. In inhalation studies with BaP, formaldehyde, benzene, nickel, and cadmium, lung tumors were observed only with a massive dose of BaP, far in excess of that to which humans are exposed from MS or ETS. As noted previously, these BaP findings were rated as "equivocal" by the RTECS. None of the inhalation studies with formaldehyde, benzene, or nickel produced lung tumors of the type reported to be associated with cigarette smoking. Takenaka *et al.* (1983) reported dose-related adenocarcinomas and squamous cell carcinomas in rats treated via inhalation with high levels of various cadmium chloride aerosols.

Aviado (1990) also discussed several miscellaneous MS and/or SS components suspected of being carcinogenic to humans based on observations in humans. For the MS components 2-toluidine, formaldehyde, hydrazine, and cadmium [listed as tumorigens by Hoffmann and Hecht (1990), EPA (1992), and OSHA (1994)], there is insufficient evidence from epidemiological studies to support any association between these smoke components and human lung cancer.

As noted in **Table 4**, at various times the IARC has evaluated the evidence for carcinogenicity of several of the tobacco components listed. In many instances, the IARC has not issued its evaluation. The IARC's evaluations in general are based on the results from experimental studies involving administration of the material in question at levels substantially higher than those encountered in MS, SS, or ETS.

With regard to crotonaldehyde, listed by Hoffmann and Hecht (1990), Aviado (1990) noted that it was one of the

> [M]iscellaneous substances [which does] not have supporting human studies and suspicion of carcinogenicity is entirely based on experimental animal observations... The dermal route has been used for the following compounds resulting in tumor initiation, promotion or cocarcinogenic

activity: catechol, crotonaldehyde, phenol, hydroquinone and 3-vinylpyridine.

Aviado's comments are also a meaningful adjunct to recent statements such as those by Peto and Doll (1985) who wrote that:

> 30 years of laboratory research has yet to identify reliably the important carcinogenic factors in cigarette smoke.

and by the IARC (1986) which noted:

> This complexity [of tobacco smoke] has made it difficult to identify any individual agent within tobacco smoke as the chief cause of any of the diseases that are caused by smoking.

The data presented here and by Rodgman (1992) demonstrate that it is inappropriate to use tables such as those listing ''Tumorigenic Agents in Tobacco and Tobacco Smoke'' (Hoffmann and Hecht, 1990) and ''43 Chemical Compounds Identified in Tobacco Smoke for Which There Is 'Sufficient Evidence' of Carcinogenicity in Humans or Animals'' (OSHA, 1994) as evidence of any relationship between exposure to MS and lung cancer induction in smokers or between exposure to ETS and lung cancer induction in nonsmokers.

*Skin-Painting Studies with Cigarette Smoke Condensate (CSC)*

In a continuation of the mouse skin-painting studies (Wynder *et al.*, 1953a, 1953b, 1955, 1956; Wynder and Wright, 1957) reported from 1953 to 1957, Wynder *et al.* (1957a, 1957b) examined the effect of application of lower and lower total annual doses of MS CSC on tumor production in skin-painted mice. They reported that skin painting of mice with a total annual dose of 10 g/mouse produced papilloma in about 60% of the mice; at a total annual dose of 7.5 g/mouse the percentage of papilloma-bearing animals was reduced to about 35%. Only a small percentage (< 10%) of papilloma-bearing animals (but no carcinoma-bearing) animals was observed when the total annual amount of MS CSC applied was less than 5 g/mouse; further reduction of the annual dose to 3 g/mouse resulted in no papilloma- or carcinoma-bearing mice. Thus, in this study, reduction of the total annual dose from 10 g/mouse to 3 g/mouse reduced the percentage of tumor-bearing animals from 60% to 0%. This represents a 3.3-fold reduction in the dose of the applied material, CSC.

These data from the dose-response study (and the threshold limit value for MS CSC) were subsequently reported several times by Wynder and Hoffmann (1962a, 1963b, 1964, 1967) who stated in 1964 and again in 1967:

> It is apparent that a reduction of tumorigenic components can be most readily accomplished by reducing the total amount of smoke condensate...to which one is exposed.

Wynder and Hoffmann (1965) determined the effect of MS CSC dose on tumor yield by conducting lifetime skin-painting studies in mice (50 mice per dilution) with various dilutions of CSC-acetone suspensions. Skin painting with a fixed volume of successive dilutions of a 50% CSC-acetone suspension reduced the percent tumor-bearing animals from 45% with a 50%

suspension to 34% with a 33% suspension, to 20% with a 25% suspension, to 8% with a 10% suspension, and to 2% (one tumor-bearing mouse) with a 5% suspension, *i.e.*, a 10-fold dilution of the CSC-acetone suspension produced a 25-fold diminution in % tumor-bearing animals. From their results, Wynder and Hoffmann (1965) noted:

> It is apparent...from laboratory studies...that exposure to tobacco smoke condensate and tumor yield are quantitatively correlated.

A few years earlier, Wynder (1961) had commented on the effect of dose reduction on tumor yield in laboratory animals painted with CSC. Because he used much more reasonable doses of CSC in his skin painting, Passey in England was unable to confirm the findings of Wynder *et al.* (1953a, 1953b). Wynder's explanation was as follows:

> What really happened was that Passey applied too weak a concentration of tobacco smoke condensate to his animals. Of course, since tobacco smoke is only a weak carcinogen to begin with, if you dilute its concentration too markedly, it is no wonder that you do not obtain any cancer. It would be just like a human being smoking one or two cigarettes a day without inhaling it. His risk of developing lung cancer would certainly also not be greater than that of a non-smoker...
>
> [From] a study which we have done on the dose response of different amounts of smoke condensate to the production of skin cancer in mice... [y]ou will note that, if we applied to the mouse 5 g or less per year of tobacco smoke condensate we were not able to produce any cancers. This of course explains the failure of Dr. Passey to repeat our work. But it clearly shows that tobacco smoke condensate is not a very strong carcinogen.

The importance of dose (exposure) was reiterated in the same language by Wynder and Hoffmann in their lengthy 1964 review article (Wynder and Hoffmann, 1964) and 1967 book (Wynder and Hoffmann, 1967) on tobacco and tobacco smoke:

> Since 1953, when the first large-scale production of epidermoid cancer was reported, many investigators have verified these findings. *Some negative findings* (Shotadze, 1953; Gwynn, 1954; Passey *et al.*, 1954; Kakhiani, 1955; Hamer and Woodhouse, 1956; Gwynn and Salaman, 1956) *are largely, if not exclusively, a result of inadequate dose.* (*Emphasis added:* AR)

Wynder and Hoffmann (1964, 1967) also noted that Gritsiute and Mironova (1960) reported only 3 (1.7%) tumor-bearing animals (TBA) out of 174 treated with between 1.4 and 2.6 g of CSC over a 10-month period whereas their own studies gave 44% TBA treated with 11.7 g CSC over a 15-month period. When the difference in treatment time is disregarded, a dose reduction ranging from 4.5 to 8 reduced the % TBA by a factor of 26! Findings such as this plus those discussed below should have been considered by OSHA in its assessment of the extremely dilute system represented by ETS.

From the late 1960s to the late 1970s, the National Cancer Institute (NCI) in conjunction with the Tobacco Working Group (TWG) conducted a massive 10-year ''less hazardous-cigarette study'' involving tests on the MS CSC from nearly 100 experimental cigarettes and over 30 control cigarettes [Standard Experimental Blends (SEB)] and the Kentucky 1R1 Reference

Cigarette. In the mouse skin-painting studies, it was found that reduction of the applied dose from 50 mg/mouse/day to 3 mg/mouse/day produced a 25-fold reduction, and in one instance a 50-fold reduction, in percent tumor-bearing animals, *i.e.*, the equivalent of a 17-fold dilution in applied CSC produced a 25- to 50-fold reduction in % tumor-bearing animals. The NCI data (Gori, 1976b, 1976d, 1977b, 1980b; NCI, 1980) on the effect of skin-painting dose on % tumor-bearing animals (TBA) are summarized in **Table 18**.

The results of a comparison of the tumorigenic activity of MS CSC *vs* that of SS CSC were reported by Mohtashamipur *et al.* (1990). On the basis of the levels of reported carcinogenic and genotoxic compounds in cigarette MS and SS as listed by Grimmer *et al.* (1977a, 1977b, 1987) and by Hoffmann *et al.* (1987), Mohtashamipur *et al.* (1990) estimated that the tumorigenicity of SS CSC on a gram-for-gram basis would be from 10 to 50 times that of MS CSC. However, their experimental data indicated only a 2- to 6-fold difference.

The experimental protocol for the skin-painting study by Mohtashamipur *et al.* is substantially different from that used in a great many studies over the past four decades; *cf.* protocols described by Wynder and Hoffmann (1967) and that used in the NCI Smoking and Health Study as described by Gori (1976a, 1976b, 1977, 1980) and the NCI (1980). The protocol in the study by Mohtashamipur *et al.* was as follows: The MS CSC or the SS CSC at three weekly dose levels (5, 10, and 15 mg) was administered at half-dose levels twice weekly for 3 months to the shaved backs of female mice (MNRI strain). After completion of the skin-painting regime by the end of the 3-month painting period, the animals were observed for the remainder of their lifespan. The mean lifespan for the MS CSC-treated mice was 17.8±4.3 months (range 18-20 months); that for the SS CSC treated mice was 16.7±4.7 months (range 17-18 months).

**Table 19** summarizes the data reported by Mohtashamipur *et al.* (1990) on the comparison of MS CSC *vs* SS CSC tumorigenicity.

These data indicating carcinoma production by administration of 195 mg (0.195 g) of MS CSC over a 3-month (13-week) period appear to be in direct conflict with the earlier data of Wynder *et al.* (1957a, 1957b) who showed that a total annual MS CSC dose less than 3 g elicited neither papilloma nor carcinoma in the CSC-treated animals.

## TABLE 18: NCI TWG STUDIES: % TUMOR-BEARING ANIMALS vs DAILY DOSE

Percent Tumor-Bearing Animals at Daily Skin-Painting Dose, mg

| Cigarette (Study No.) | 50 | 40 | 25 | 12.5 | 10 | 06 | 03 | Reference |
|---|---|---|---|---|---|---|---|---|
| UK 1R1 (1st) | 34 | .. | 48 | .. | .. | .. | .. | Gori (1976a) |
| UK 1R1 (2nd) | 45 | .. | 53 | .. | .. | .. | .. | Gori (1976b) |
| UK 1R1 (3rd) | .. | .. | 49 | 18 | .. | .. | .. | Gori (1977) |
| UK 1R1 (4th) | .. | .. | 62 | 33 | .. | .. | .. | Gori (1980) |
| SEB I (1st) | 43 | .. | 41 | .. | .. | .. | .. | Gori (1976) |
| | 51 | .. | 41 | .. | .. | .. | .. | Gori (1976) |
| | 35 | .. | 47 | .. | .. | .. | .. | Gori (1976) |
| | 49 | .. | 50 | .. | .. | .. | .. | Gori (1976) |
| | 47 | 48 | 44 | .. | 28 | .. | .. | Gori (1976) |
| Average | 45.0 | .. | 44.6 | .. | .. | .. | .. | |
| SEB I (2nd) | 60 | .. | 55 | .. | .. | .. | .. | Gori (1976b) |
| SEB I (3rd) | .. | .. | 51 | 19 | .. | 2 | 2 | Gori (1977) |
| SEB II (2nd) | 54 | .. | 50 | .. | .. | .. | .. | Gori (1976b) |
| | 40 | .. | 52 | .. | .. | .. | .. | Gori (1976b) |
| | 49 | .. | 41 | .. | .. | .. | .. | Gori (1976b) |
| | 50 | .. | 47 | .. | .. | .. | .. | Gori (1976b) |
| Average | 48.3 | .. | 47.5 | .. | .. | .. | .. | |

## TABLE 19: COMPARISON OF TUMORIGENICITY OF MAINSTREAM CIGARETTE SMOKE CONDENSATE (MS CSC) vs SIDESTREAM CIGARETTE SMOKE CONDENSATE (SS CSC)

| Dose | | MS CSC | | | SS CSC | | |
|---|---|---|---|---|---|---|---|
| mg/wk | total mg | Initial No. | P | C | Initial No. | P | C |
| 5 | 65 | 70 | 0 | 2[a] | 70 | 1 | 3 |
| 10 | 130 | 70 | 0 | 0 | 70 | 2 | 1 |
| 15 | 195 | 70 | 0 | 3 | 70 | 11 | 6 |

[a] Two malignant non-carcinomatous tumors: 1 sarcoma, 1 Schwannoma.

*Skin-Painting Studies with Individual PAH Components of CSC*

In addition to data showing that progressive diminution of the applied dose of MS CSC eventually results in a dose ineffective in tumor production in the CSC-treated animals, there are data showing that essentially the same results are obtained when laboratory animals are treated with smaller and smaller doses of several of the individual PAH components of MS CSC. This has been shown with PAHs, *e.g.*, BaP, DBA, considered sufficiently tumorigenic to be listed by OSHA (1994), EPA (1990a), and Hoffmann and Hecht (1990) as tobacco smoke "tumorigens."

While not a mouse skin-painting study, Dobrowolskaia-Zavadskaia (1938) demonstrated that subcutaneous injection of 10 $\mu$g (10,000 ng) of DBA induced sarcoma at the site of injection in 11% of the 328 mice injected. The % tumor-bearing animals decreased as the injected dose was decreased. When the injected dose was 1 $\mu$g (1000 ng) of DBA, none of 156 injected mice developed sarcoma.

Early experiments by Sall and Shear (1940) with BaP had produced no tumors via skin painting at concentrations below 0.02%; Gottschalk (1942) demonstrated that subcutaneous injection of at least 0.4 $\mu$g (400 ng) of BaP was required for tumor development. In almost all experiments with PAHs such as BaP or DBA, subcutaneous injection of an effective tumor-generating dose results in development of sarcoma not carcinoma at the site of injection; skin painting with these PAHs generally produces papilloma and carcinoma at the site of application.

Citing previously reported well-established findings by Shimkin, Andervont, Bryant, and others that the concentration of an injected carcinogen had a direct relation to the incidence and the latent period of subcutaneously induced tumors, Wynder *et al.* (1957) undertook a skin-painting study

> [T]o establish the minimum dose of benzopyrene capable of producing skin cancers in mice and rabbits with the same technique of application employed in previous studies [Wynder *et al.* (1953a, 1953b, 1956); Graham *et al.* (1957)].

The previous studies cited were those by Wynder and his colleagues on the production of carcinoma in mice or rabbits by skin painting with cigarette "tar" (or MS CSC).

Data collected on the effect of variously diluted solutions of BaP on mouse epithelium are summarized in **Table 20** for the Swiss strain mouse. Data obtained with the CAF1 and C57BL mouse strains showed essentially the same results, *i.e.*, no significant differences in tumor susceptibility were found among the three mouse strains. The data obtained from the BaP treatment of rabbits with variously diluted solutions of BaP not only indicated there was a dose at and below which no tumors developed but also indicated a significant difference in species esponse: The rabbit was much less susceptible to tumor induction by BaP than the mouse, a

**TABLE 20: PAPILLOMA AND CARCINOMA PRODUCTION BY BENZO[*a*]PYRENE IN SKIN-PAINTED MICE (SWISS STRAIN)**

Percent Benzo[*a*]pyrene in Acetone (w/v) in Studies by

| No. of Weeks of Application | Wynder *et al.*, (1957) | | | Hecht *et al.*, (1976) | | | Wynder *et al.*, (1957) | | | Hecht *et al.*, (1976) | | | Wynder *et al.*, (1957) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.01 | | | 0.01 | | | 0.005 | | | 0.005 | | | 0.001 | | | 0.0005 | | | 0.0001 | | |
| | S[a] | P | C | S | P | C | S | P | C | S | P | C | S | P | C | S | P | C | S | P | C |
| 4.3 | 20 | 0 | 0 | | | | 20 | 0 | 0 | | | | 20 | 0 | 0 | 20 | 0 | 0 | 20 | 0 | 0 |
| 8.7 | 20 | 0 | 0 | | | | 19 | 0 | 0 | | | | 20 | 0 | 0 | 20 | 0 | 0 | 20 | 0 | 0 |
| 10 | | | | 20 | 0 | 0 | | | | 20 | 0 | 0 | | | | | | | | | |
| 13 | 20 | 1 | 0 | | | | 19 | 0 | 0 | | | | 20 | 0 | 0 | 20 | 0 | 0 | 19 | 0 | 0 |
| 17.3 | 20 | 3 | 0 | | | | 19 | 0 | 0 | | | | 20 | 0 | 0 | 20 | 0 | 0 | 19 | 0 | 0 |
| 20 | | | | 19 | 0 | 0 | | | | 20 | 0 | 0 | | | | | | | | | |
| 21.7 | 20 | 3 | 0 | | | | 19 | 0 | 0 | | | | 20 | 0 | 0 | 20 | 0 | 0 | 19 | 0 | 0 |
| 25 | | | | 19 | 1 | 0 | | | | 20 | 0 | 0 | | | | | | | | | |
| 26 | 19 | 3 | 0 | | | | 19 | 0 | 0 | | | | 19 | 0 | 0 | 20 | 0 | 0 | 19 | 0 | 0 |
| 30.3 | 19 | 9 | 3 | | | | 16 | 2 | 0 | | | | 19 | 0 | 0 | 17 | 0 | 0 | 18 | 0 | 0 |
| 34.7 | 11 | 17 | 8 | | | | 15 | 3 | 1 | | | | 19 | 0 | 0 | 17 | 0 | 0 | 18 | 0 | 0 |
| 35 | | | | 18 | 10 | 0 | | | | 20 | 1 | 1 | | | | | | | | | |
| 39 | 8 | 17 | 10 | | | | 13 | 3 | 1 | | | | 18 | 0 | 0 | 17 | 0 | 0 | 18 | 0 | 0 |
| 43.3 | 8 | 17 | 13 | | | | 11 | 4 | 2 | | | | 16 | 0 | 0 | 17 | 0 | 0 | 18 | 0 | 0 |
| 45 | | | | 14 | 18 | 7 | | | | 17 | 3 | 1 | | | | | | | | | |
| 47.7 | 1 | 17 | 16 | | | | 10 | 7 | 3 | | | | 16 | 0 | 0 | 14 | 0 | 0 | 18 | 0 | 0 |
| 52 | 0 | 17 | 17 | | | | 9 | 8 | 5 | | | | 15 | 0 | 0 | 14 | 0 | 0 | 16 | 0 | 0 |
| 55 | | | | 0 | 18 | 16 | | | | 15 | 9 | 2 | | | | | | | | | |
| 56.3 | | | | | | | 3 | 9 | 9 | | | | 13 | 0 | 0 | 14 | 0 | 0 | 15 | 0 | 0 |
| 60.7 | | | | | | | 2 | 11 | 10 | | | | 11 | 0 | 0 | 12 | 0 | 0 | 13 | 0 | 0 |
| 62 | | | | | | | | | | 12 | 10 | 7 | | | | | | | | | |
| 65 | | | | | | | 2 | 11 | 11 | | | | 7 | 0 | 0 | 12 | 0 | 0 | 11 | 0 | 0 |
| 69.3 | | | | | | | 1 | 11 | 11 | | | | 7 | 0 | 0 | 11 | 0 | 0 | 9 | 0 | 0 |
| 78 | | | | | | | 0 | 11 | 11 | | | | 6 | 0 | 0 | 7 | 0 | 0 | 4 | 0 | 0 |
| 82.3 | | | | | | | | | | | | | 4 | 0 | 0 | 4 | 0 | 0 | 1 | 0 | 0 |
| 86.7 | | | | | | | | | | | | | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| 91 | | | | | | | | | | | | | | | | 0 | 0 | 0 | | | |

[a] S = number of surviving mice; P = number of mice with papilloma; C = number of mice with carcinoma

finding previously demonstrated by Berenblum and Schoental (1947)[f]. Carcinoma production in rabbits required skin-painting with a solution of 0.5% BaP in acetone. No carcinoma was induced in the rabbits when the painting solution was 0.005% BaP. **Table 20** shows the Swiss mouse response to this dose level: 11 of 20 Swiss mice with carcinoma. The percentages of carcinoma-bearing animals with the 0.005% BaP solution were as follows: rabbit, 0; Swiss mouse, 55%; CAF[1] mouse, 85%; C57BL mouse, 75%.

Wynder, Fritz, and Furth (1957) stated:

> From the practical point of view, the most striking feature of the present study is the fact that a five-fold dilution of a 0.005 percent benzopyrene solution [*i.e.*, from 0.005% to 0.001%] in acetone changes the response from one where nearly all the animals develop cancer to one where very few[1] develop cancer.
>
> 1 At a dose level of 0.001% BaP, neither the Swiss nor the C57BL mouse strains nor the rabbits showed any papillomas or carcinomas.

Although the authors did not comment on the fact that a 10-fold dilution of the 0.005% BaP solution (*i.e.*, from 0.005% to 0.0005% BaP failed to produce malignant tumors in either the three mouse strains or the rabbits, they did note that the MS CSC used in their previous skin-painting studies showed a BaP concentration of no more than 2 ppm, *i.e.*, 2 $\mu$g of BaP per gram of CSC. A 50% MS CSC-acetone (w/v) solution would contain 1 $\mu$g of BaP per ml, approximately a 0.0001% solution with respect to BaP. In their discussion, Wynder *et al.* (1957) wrote that their results confirmed the views and findings of Kennaway (1948) and Poel (1956):

> [T]here is obviously a level below which even lifelong exposure to a given amount of a carcinogen will not produce tumors in experimental animals.

More recently, Hecht *et al.* (1976) studied tumor generation in Swiss strain mice skin painted at two dose levels (0.01% or 0.005%) for 62 weeks with acetone solutions of BaP. Their results with respect to tumor generation, also shown in **Table 20**, essentially agreed with those of Wynder *et al.* (1957) for the 0.01% and 0.005% solutions. However, the survival rate for the mice treated with the 0.005% BaP solution in the study by Hecht *et al.* was much greater at the end of 62 weeks than that for the mice similarly treated in the study by Wynder *et al.*

The phenomenon of absence of tumor production at extremely low dose levels is not confined to MS CSC or its PAH components. Similar effects have been observed and reported in comparable studies with carcinogenic amines such as the aminoazo dyes: Reduction of their dose level by limitation of the administered dose or by suitable dilution of the compound under study eventually reached a dose level at which no tumors were produced during the course of the experiment, usually the lifespan of the animal (Miller and Miller, 1953).

---

[f] Berenblum and Schoental (1947) determined that the rabbit and the mouse were equally susceptible to the tumorigenicity of coal tar but the rabbit was much less susceptible to the tumorigenicity of BaP than the mouse and much more susceptible to the tumorigenicity of certain coal tar fractions than the mouse.

MS CSC does not contain aminoazo compounds *per se* but does contain amines whose biological properties observed in laboratory animals are somewhat similar to those of the aminoazo compounds.

### *Ciliastasis Studies*

The inability to explain less than 2% of the biological response in laboratory animals skin-painted with CSC solutions on the basis of its content of known tumorigens, promoters, and cocarcinogens led to the incorporation into the theory of tobacco smoke tumorigenesis the concept of respiratory tract ciliastasis: It was proposed that impairment of ciliary action would result in prolonged exposure of the ciliated tissue to the inhaled particle and the tumorigens contained therein.

Wynder and Hoffmann (1964, 1967) commented on this as follows:

> All studies reported to date have shown that cigarette smoke affects the metachronic activity of cilia, a motion that is necessary to propel the viscid mucoid mass. During inhalation, in the absence of effectively beating cilia, mucus flow slows down and perhaps stops. At that time, components in cigarette smoke may act upon the underlying cells, as can the entrapped particles.

Wynder and Hoffmann commented several times on the fact that most of the known ciliastatic components of MS demonstrated to be ciliastatic in various *in vitro* systems were water soluble and this property would markedly influence their fate and behavior during and after inhalation. In 1965, they noted (Wynder and Hcffmann, 1965):

> As far as human smoking habits are concerned, it remains also to be estimated to which extent volatile smoke components reach the bronchial tree. Preliminary studies indicate that a significant proportion of the gaseous components is being retained within the oral cavity.

and in 1967 (Wynder and Hoffmann, 1967):

> Water-soluble volatile components, which are primarily responsible for the results of the acute *in vitro* short-term cilia toxicity tests, are, to a large extent, removed when cigarette smoke contacts the saliva in the mouth and the abundant secretions of the trachea and main bronchi.

The topic dealing with ciliastasis and MS ciliastats (from testing in *in vitro* systems) is of particular interest with respect to the ETS situation because of the data showing:

- The major ciliastats in tobacco smoke are water soluble. These include the ciliastats formaldehyde, acetaldehyde, crotonaldehyde, ethyl carbamate, and hydrazine[s], water-soluble tobacco smoke components that appear as tumorigens on the two "Lists of 43" **(Table 4)**.

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[s] Other water-soluble tobacco smoke components categorized as ciliastats on the basis of *in vitro* test results include ammonia, hydrogen cyanide, acrolein, acetone, nitrogen dioxide, low molecular weight phenols. The phenols are distributed between the particulate and vapor phases of tobacco smoke.

- Dose reduction (effectively, dilution) of MS or some of its "ciliastatic" components or ciliastatic fractions eventually results in a dose or concentration level at which no ciliastasis is produced in the *in vitro* systems used.

- A large proportion of the inhaled MS components categorized as ciliastats (and in some instances as tumorigens) does not reach the ciliated areas of the respiratory tract because of their removal from the smoke stream during passage over the moist tissues of the mouth and trachea (Dalhamn *et al.*, 1968a, 1968b; Rodgman *et al.*, 1964).

- Ciliastatic compounds inhaled nasally are removed from the inhaled gas stream by "resorption." This raises the question as to how much formaldehyde or acetaldehyde or crotonaldehyde in ETS, an already extremely dilute system, will reach the lung whether inhaled orally or nasally! Are the levels of these tobacco smoke components in ETS sufficient for these compounds to be included on the "Lists of 43?"

### *Ciliastasis Studies with CSC Fractions*

Wynder and Hoffmann (1962b, 1963a) in their study in mussels of the ciliastatic activity of aqueous extracts of various fractions of smoke condensate demonstrated that reduction of the applied dose of each of the fractions tested eventually changed the ciliastasis from "immediate and complete" to "none." Their findings are summarized in **Table 21.**

**TABLE 21: CILIARY ACTIVITY, CIGARETTE SMOKE FRACTIONS, AND DOSE LEVEL**

| Cigarette Smoke Fraction From Which Aqueous Extract Was Obtained | % of Smoke[a] | Immediate & Complete Ciliastasis at Dc[b] | Complete Ciliastasis in 10-40 min at D10 | No Apparent Ciliastasis at Do | Dc/Do |
|---|---|---|---|---|---|
| Phenolic fraction | 9.3 (16.0)[d] | 0.03 | 0.015 | 0.002 | 15 |
| Acidic fraction[c] | 2.2 (11.0) | 0.04 | 0.02 | 0.007 | 6 |
| Neutral fraction | 47.2 (0.9) | ... | 0.27 | 0.034 | 8[e] |
| "Insoluble" fraction | 14.0 (20.0) | 1.1 | 0.55 | 0.055 | 20 |
| Basic fraction | 8.7 (65.0) | 1.95 | 0.98 | 0.08 | 24 |

[a] The unit for Dc, D10, and Do is gram/100 ml.
[b] The values for each fraction as a percentage of total smoke condensate were previously described by Wynder and Hoffmann (1961a, 1961b).
[c] Phenol-free.
[d] Number in parentheses is percentage of smoke fraction that is soluble in water.
[e] Value for D10/Do.

Calculation of the ratio Dc/Do, where Dc is the dose producing "immediate and complete" ciliastasis and Do is the dose producing "zero" ciliastasis, gives values ranging from 6 to 24, *i.e.*, a 24-fold dilution of every MS CSC fraction tested in this study resulted in or

would result in a non-ciliastatic situation.

The data in **Table 21**, originally reported at the annual AACR meeting by Wynder and Hoffmann (1962b), were subsequently published, but in less detail, by Wynder and Hoffmann (1963a) in 1963.

*Ciliastasis Studies With Individual Cigarette Smoke Components*

Examination of the *in vitro* ciliastasis produced by a variety of MS components reveals that for all components studied there is a level below which no ciliastasis is observed. Guillerm *et al.* (1961) studied the effect of various MS components in the *in vitro* system, ciliated rat trachea. Concentrations less than those shown in **Table 22** produced no ciliastasis in ciliated rat trachea. All of the compounds listed in **Table 22** are primarily vapor-phase components of MS.

**TABLE 22: LOWEST CONCENTRATIONS IN RINGER SOLUTION LEADING TO CILIASTASIS IN CILIATED RAT TRACHEA**

| Compound | Concentration, µg/L |
|---|---|
| acrolein | 90 |
| formaldehyde[a] | 200 |
| acetaldehyde[a] | 3,000 |
| propionaldehyde | 3,500 |
| isobutyraldehyde | 4,500 |
| 2-furaldehyde | 7,500 |
| butanone | 80,000 |
| acetone | 100,000 |

[a] On the "Lists of 43" (Table 4)

Wynder and Hoffmann (1963a) in their study of the phenolic components of cigarette smoke also reported that reduction of the concentrations of solutions of the simple phenols (phenol, *o*-cresol, *m*-cresol, *p*-cresol, *o*-ethylphenol, 2,4-dimethylphenol) from 1.0% to 0.05% (a 20:1 dilution) reduced the ciliary activity of each solution in an *in vitro* system to zero:

> At the highest concentration (1.0%), the phenol derivatives demonstrated greater ciliastatic effects than did phenol itself. At the lowest concentrations tested (0.05%), none of the phenols induced ciliastasis.

***Nose Inhalation of ETS* vs *Mouth Inhalation of MS***

Rodgman (1991, 1992) discussed the effect of water solubility of tobacco smoke components reported to be ciliastatic in *in vitro* systems on the ultimate exposure of the smoker's lungs to MS or the nonsmoker's lungs to ETS.

Early in the study of the effect of MS components on ciliary activity, it was realized that all of the MS components (formaldehyde, acetaldehyde, acrolein, hydrogen cyanide, formic acid,

acetic acid, etc.) that produced ciliastasis in *in vitro* systems were water-soluble. This observation led to proposals (Dalhamn and Sjoholm, 1963; Dalhamn and Rylander, 1964; Rodgman *et al.*, 1964; Wynder, 1964; USPHS, 1964; Wynder *et al.*, 1965a, 1965b; Wynder and Hoffmann, 1967, 1968) that this water solubility would result in removal of substantial amounts of the *in vitro* ciliastatic components from the MS by their solution in the aqueous fluids coating the surfaces of the oral cavity and trachea during the time that the MS was held in and/or traversed these portions of the respiratory tract. The levels of ciliastats reaching the ciliated areas in the smoker's lower respiratory tract would produce insignificant ciliastasis, if any at all. This ''scrubbing'' of ciliastatic components from the inspired MS stream was demonstrated in smokers by Rodgman *et al.* (1964) and Dalhamn *et al.* (1968a). Nasally inhaled components are removed in the nasal cavity by ''resorption'', a process similar to the ''scrubbing'' of water-soluble components from gas streams such as MS VP.

In his studies of the ciliastatic activity of sulfur dioxide, subsequently identified as a minor tobacco smoke VP component (Terrell and Schmeltz, 1970), Dalhamn (1961) demonstrated that sulfur dioxide was a powerful ciliastat *in vitro* at or below 100 ppm but did not produce ciliastasis *in vivo* at or below 100 ppm because much of the sulfur dioxide was removed in the nasal cavity. Dalhamn found that in rabbits exposed to 300, 200, and 100 ppm of sulfur dioxide, the percentage showing cessation of ciliary activity within 45 minutes was 90, 60, and 0, respectively. Removal of inhaled components in the nasal cavity, termed ''resorption,'' is similar to the ''scrubbing'' of water-soluble components from gas streams, *e.g.*, MS VP. This nasal resorption is an important process not only from a ciliastasis-MS component point of view but also from an ETS point of view since ETS, in contrast to MS which is primarily inhaled via the mouth, is inhaled primarily through the nose. ETS VP components that would be removed through resorption in the nasal cavity include formaldehyde, acetaldehyde, crotonaldehyde, hydrazine, and possibly ethyl carbamate, five MS components listed by Hoffmann and Hecht (1990) as ''tumorigens'' in MS. Thus, very little, if any, of these water-soluble components, already highly diluted in ETS, would reach the lungs and the ciliated tissue to be involved in lung cancer causation attributed to ETS by some authors. As noted by Aviado (1990), data from inhalation studies in animals indicate it is unlikely that either formaldehyde or hydrazine contribute to pulmonary carcinogenesis.

Dalhamn and Rylander (1965) commented on the possible differences in the effects produced by mouth inhalation *vs* nose inhalation of tobacco smoke:

> The most important point is probably that the smoke is administered through the mouth. If smoke is administered through the nose quite different absorption conditions are present, and it is likely that the smoke which enters the lungs differs considerably from that inhaled through the mouth. This could also be one of the factors which explains why in animal experiments no tumor-producing effects have been found by tobacco smoke in inhalation studies where the smoke was administered through the nose.

In 1968, Dalhamn *et al.* published the results of their studies with humans on the mouth absorption (1968a) and lung retention (1968b) of various components of cigarette smoke. As noted earlier, the findings that a substantial percentage of the levels of MS water-soluble

components demonstrated to be ciliastatic *in vitro* is absorbed in the oral cavity lessened the interest in ciliastasis produced by MS components. The data generated by Dalhamn *et al.* also served a second useful purpose in that they demonstrated:

- The remarkable difference, albeit with respect to only a few MS smoke components, between the compositions of inhaled and exhaled MS, and
- All of the few components measured in the inhaled MS were found in the exhaled MS, *i.e.*, none was 100% retained in the lungs, etc. nor 100% absorbed in the oral cavity.

These data are summarized in **Tables 23** and **24**. It is obvious that mouth absorption of such water-soluble ciliastats as acetaldehyde (60%) and acetone (56%) is substantial **(Table 23)**; whereas, the mouth absorption of the relatively water-insoluble components isoprene (20%), toluene (28%), and CO (3%) is much less.

**TABLE 23: LUNG RETENTION AND MOUTH ABSORPTION OF SEVERAL CIGARETTE MS COMPONENTS**

| | Per Cigarette MS | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Inhalation into Lungs | | | Held in Mouth for 2 sec. | | |
| Smoke Component | Delivery | Retention | % | Exhaled | Absorbed in Mouth[a] | % | Exhaled |
| acetaldehyde, $\mu g$ | 940 | 930 | 99 | 10 | 560 | 60 | 380 |
| acetone, $\mu g$ | 570 | 490 | 86 | 80 | 320 | 56 | 250 |
| acetonitrile, $\mu g$ | 320 | 282 | 91 | 28 | 230 | 74 | 80 |
| isoprene, $\mu g$ | 560 | 554 | 99 | 6 | 110 | 20 | 450 |
| toluene, $\mu g$ | 250 | 232 | 93 | 18 | 70 | 28 | 180 |
| CO, mg | 30.0[b] | 16.2 | 54 | 13.8 | 0.9 | 3 | 29.1 |
| TPM, mg | 30.0 | 28.8 | 96 | 1.2 | 4.8 | 16 | 25.2 |

[a] No inhalation

[b] Per cigarette CO delivery assumed to be the same as per cigarette TPM delivery.

The data in **Table 24** are derived from those of Dalhamn *et al.* (1968a, 1968b): The change in the composition of the MS delivered by the cigarette to the composition of the MS exhaled by the smoker is readily seen from the ratios, *e.g.*, acetaldehyde is inhaled by the smoker at a ratio of 31.3 $\mu g$/mg TPM but is exhaled at a ratio of 8.3 $\mu g$/mg TPM; acetone is inhaled at a ratio of 19.0 $\mu g$/mg TPM but exhaled at a ratio of 66.7 $\mu g$/mg TPM. Similarly, the MS composition is altered by holding the smoke in the mouth without inhalation. Since these exhaled smokes — whether originally inhaled, held in the mouth with no or minimal inhalation, or some blend of both (inhalation and mouth retention) — ultimately contribute to ETS, it is obvious that the contribution is not equivalent quantitatively to the MS originally generated by the cigarette.

TABLE 24: **DIFFERENCE BETWEEN COMPOSITION OF INHALED AND EXHALED MS AND BETWEEN MOUTH-HELD AND EXHALED MS**

| | Per Cigarette Ratios, $\mu$g/g TPM or mg/g TPM | | |
|---|---|---|---|
| Smoke Component | Delivery Ratio | Inhalation into Lungs & Exhaled, Exhaled MS Ratio | Held in Mouth for 2 sec.[a] & Exhaled, Exhaled MS Ratio |
| acetaldehyde, $\mu$g | 31.3 | 8.3 | 15.1 |
| acetone, $\mu$g | 19.0 | 66.7 | 9.9 |
| acetonitrile, $\mu$g | 10.3 | 23.3 | 3.2 |
| isoprene, $\mu$g | 18.7 | 5.0 | 17.9 |
| toluene, $\mu$g | 8.3 | 15.0 | 3.2 |
| CO, mg | 1.0[b] | 11.5 | 1.15 |
| TPM, mg | 1.0 | 1.0 | 1.0 |

[a] No inhalation

[b] Per cigarette CO delivery assumed to be the same as per cigarette TPM delivery

The data presented by Dalhamn *et al.* (1968a, 1968b) on lung retention of MS components were similar to data reported in 1951 by Laskowski (1951) and to data on lung retention and mouth absorption of ciliastats by Rodgman *et al.* in 1964. The various sets of data are summarized in **Table 25**. Each set of data indicates that exhaled MS is substantially different *quantitatively* from the inhaled MS.

If MS is mouth inhaled and held for any length of time (a few seconds) in the mouth prior to being drawn into the lungs, some of the MS water-soluble VP components are ''scrubbed'' from the smoke stream and reach the ciliated areas at much reduced concentrations. This is also true to a lesser degree for water-soluble components of the particulate phase (see **Tables 23-25**). The exposure of the lungs to MS entities alleged to be tumorigenic will be much less than some authors claim. Similarly, in nose inhalation of ETS, some of its water-soluble components (formaldehyde, acetaldehyde, crotonaldehyde, ethyl carbamate, hydrazine) — alleged to be tumorigenic at the levels in MS — will be ''resorbed'' in the nasal cavity and reach ciliated areas at concentrations reduced not only by the ''resorption'' mechanism but also by the dilution inherent in ETS generation from exhaled MS and SS produced during inter- and intrapuff smoldering. The exposure of the lungs to these ''tumorigens'' will obviously be substantially less than some writers claim.

Thus, these mechanisms — ''scrubbing'' and ''resorption'' — effective in substantially diminishing the amounts of MS water-soluble *in vitro* ciliastats that reach the lung during active smoking will be operative during ETS inhalation, whether oral or nasal, and diminish the amounts of the same and similar ETS components that reach the lung. This diminution in amounts will be particularly pertinent in the case of the smoke components formaldehyde, acetaldehyde, crotonaldehyde, ethyl carbamate, and hydrazine on the ''Lists of 43.''

**TABLE 25: LUNG RETENTION AND MOUTH ABSORPTION DATA**

| | % Retention or Absorption | | | | | |
|---|---|---|---|---|---|---|
| | Laskowski (1951) | | Rodgman *et al.* (1964) | | Dalhamn *et al.* (1968a, 1968b) | |
| Smoke Component | LR[a] | MA[a] | LR | MA | LR | MA |
| aldehydes & ketones[b] | 99 | .... | 80-90 | 40-67 | .... | .... |
| acetaldehyde | ....[c] | .... | .... | .... | 99 | 60 |
| acetone | .... | .... | .... | .... | 86 | 56 |
| acetonitrile | .... | .... | .... | .... | 91 | 74 |
| isoprene | .... | .... | 80-92 | 5-10 | 99 | 20 |
| toluene | .... | .... | .... | .... | 93 | 28 |
| TPM | .... | .... | 80-90 | 10-15 | 96 | 16 |
| nicotine | 67 | .... | .... | .... | .... | .... |
| pyridine | 98 | .... | .... | .... | .... | .... |
| ammonia | 98 | 56 | .... | .... | .... | .... |
| phenols | 57 | .... | .... | .... | .... | .... |
| carboxylic acids | 44 | .... | .... | .... | .... | .... |
| CO | .... | .... | .... | .... | 54 | 3 |

[a] LR = percentage retained in lungs; MA = percentage absorbed in mouth

[b] About 70 to 75% of the volatile aldehydes and ketones in MS is acetaldehyde plus acetone. For cigarettes in the 1950s and 1960s, the acetaldehyde:acetone ratio approximated 2:1.

[c] .... = not determined.

*ETS as a Highly Dilute System: Comparison of Biological Properties and Exposure Levels for MS, SS, and ETS*

Visual comparisons of MS, SS, and ETS reveal that these three entities are indeed different 'smokes.' Visual examination of the MS generated during the smoking of a cigarette on a laboratory smoking machine where the MS stream is visible reveals that it is obviously a concentrated ''smoke'' (or aerosol). Similarly, examination of SS in a laboratory smoking machine designed for SS collection reveals that SS is a visually dense smoke (or aerosol). Examination of SS generated during human smoking of a cigarette reveals that the SS aerosol is relatively dense adjacent to the generating site at the burning cone-tobacco rod interface and becomes more and more dilute as the SS aerosol particles move away from the cigarette. Eventually, this SS aerosol - in the process of contributing to ETS - becomes so dilute that the aerosol particles are no longer visible in ETS. Similarly, exhaled MS becomes less and less visible as it disperses after exhalation and contributes to what is defined as ETS. ETS is universally recognized as being a much more dilute system than any of its precursors, exhaled MS and intra- and interpuff-generated SS.

In the 1986 Surgeon General's report (USPHS, 1987), it was noted with respect to ETS:

> Although ETS is a far less concentrated aerosol than undiluted MS, both inhalants contain the same volatile and nonvolatile toxic agents and carcinogens...

and

> However, comparisons of MS and ETS should include the consideration of the differences between the two aerosols with regard to their chemical composition, including pH levels, and their physicochemical nature (particle size, air dilution factors, and distribution of agents between vapor phase and particulate phase). Another important consideration pertains to the differences between inhaling ambient air and inhaling a concentrated smoke aerosol during puff-drawing. Finally, chemical and physicochemical data established by analysis of smoke generated by machine-smoking are certainly not fully comparable to the levels and characteristics of compounds generated when a smoker inhales cigarette smoke.

The last sentence in this quotation is recognition that the per cigarette values reported in the literature for components in MS are the values determined for the MS issuing from the butt-end of the cigarette and presumably entering the smoker's system. Never have these machine-generated values been corrected for the portion of the MS not retained by the smoker, *i.e.*, the exhaled MS which may represent from 10 to 50% of the inhaled MS, depending on the smoker's individual smoking pattern.

In its review of ETS, the NAS-NRC (1986) compared the concentrations of 10 components of MS in MS and in indoor air where cigarette smoking was permitted. For nicotine, the concentrations ranged from 430,000 to 1,080,000 ppb for MS and ranged from 0.15 to 7.5 ppb for ETS. From these data, NAS-NRC calculated that the peak level of ETS nicotine inhaled by nonsmokers is much less than the MS nicotine inhaled by the smoker by a factor ranging from 57,333 (430,000/7.5) to 7,200.000 (1,080,000/0.15). The range 57,333 to

7,200,000 represents the dilution factor between MS inhalation and ETS inhalation for nicotine. In MS, nicotine is a particulate-phase component; in ETS, it is a vapor-phase component.

The results of similar calculations for two vapor-phase components, acrolein and acetone, of MS and ETS and for two components listed by Hoffmann and Hecht (1990), EPA (1990b), and OSHA (1994) — BaP (a particulate-phase component of both MS and ETS) and benzene (a vapor-phase component of both MS and ETS) — are summarized in **Table 26**.

**TABLE 26: DILUTION FACTORS: MS COMPONENTS INHALED BY A SMOKER *vs* ETS COMPONENTS INHALED BY A NONSMOKER BREATHING ETS-CONTAINING INDOOR AIR**

| Tobacco Smoke Component | MS/ETS Dilution Factor |
|---|---|
| nicotine | 57,333-7,200,000 |
| acrolein | 1,500-20,833 |
| benzene | 112-7,167 |
| acetone | 240-2,000 |
| benzo[*a*]pyrene | 68-40,740 |

Since the chemical and physical properties of acrolein are similar to those of the vapor-phase aldehydes listed by Hoffmann and Hecht (1990), EPA (1990b, 1992), and OSHA (1994) as tumorigens in MS (see **Table 4**: formaldehyde, acetaldehyde, crotonaldehyde), it is highly probable that their dilution factor ranges will approximate that shown for acrolein in **Table 26**. Similarly, the dilution factor ranges for the other PAHs listed as tumorigens in ETS by OSHA and EPA should approximate that for BaP.

For 20 components present in SS, Gori and Mantel (1991) estimated the number of cigarettes required to reach the Threshold Limit Values (TLV) established by the American Conference of Governmental and Industrial Hygienists (1990). Their estimates for the number of cigarettes to generate the TLV for seven components listed by OSHA (1994) and eight components listed by Hoffmann and Hecht (1990) and EPA (1990b, 1992) as tobacco smoke ''tumorigens'' are summarized in **Table 27**. The space in their calculation was assumed to be sealed, unventilated, and with a 100-$m^3$ volume.

**TABLE 27: ESTIMATED NUMBER OF CIGARETTES REQUIRED TO REACH THE THRESHOLD LIMIT VALUE (TLV) FROM SS EMISSION OF SELECTED COMPONENTS IN A SEALED, UNVENTILATED 100-$m^3$ ENCLOSURE**

| *SS Component* | *SS Output[a], mg/cigt* | *TLV[b], mg/$m^3$* | *Cigarettes Required* |
|---|---|---|---|
| cadmium | 0.0007 | 0.01 | 1,430 |
| acetaldehyde | 1.26 | 180 | 1,430 |
| benzene | 0.24 | 32 | 13,300 |
| nickel | 0.0025 | 1 | 40,000 |
| hydrazine | 0.00009 | 0.13 | 145,000 |
| benzo[*a*]pyrene | 0.00009 | 0.2[c] | 222,000 |
| 2-toluidine | 0.003 | 9 | 300,000 |
| polonium-210 | 0.4pCi | 3 pCi/L[d] | 750,000 |

[a] Data from EPA (1990a). See C-19 and 20, Table C-2.
[b] Data from ACGIH (1990).
[c] Based on TLV for coal tar pitch volatiles.
[d] EPA (1990c).

Reduction of the administered dose of CSC, CSC fractions, or individual MS components profoundly affects the biological response observed in several assays such as those involving dose administration via skin painting (carcinogenesis), via exposure of ciliated tissue (ciliastasis), or ''whole body'' or ''nose only'' exposure via inhalation with intact mammals (carcinogenesis). When an exposure at a dose level which produced a markedly high response was diminished by reduction of the dose level, the response was substantially reduced and in many instances was no longer observed. The information summarized in **Table 28** indicates that a 20- to 25-fold reduction in dose of the administered MS fractions or components generally nullified the response. In some instances, this nullification of the response was observed at a 3-fold dose reduction.

For the MS and ETS components listed, the data in **Table 26** indicate that BaP shows a dilution range, according to the NAS-NRC (1986), for MS vs ETS from 68 to 40,740, *i.e.*, the lowest dilution encountered for BaP is 68. Examination of the summarized data on skin-painting studies indicate this 68-fold dilution is more than three times the 20-fold dose reduction (100 $\mu$g to 5 $\mu$g) that diminished the response (carcinoma development) observed in BaP-painted mice from 64% to 0% tumor-bearing animals (TBA). This 68-fold dilution is nearly seven times the 10-fold dose reduction (50 $\mu$g to 10 $\mu$g) in BaP that reduced the tumor production as measured by percent tumor-bearing animals from 55% to 0%.

This diminution of observed tumorigenicity as a result of dose reduction is not limited to skin-painting studies.

In an experiment involving subcutaneous injection of dibenz[*a,h*]anthracene (DBA), it was observed that a 10-fold reduction (from 10 $\mu$g to 1 $\mu$g) in the amount of DBA injected into the

TABLE 28: SUMMARY: EFFECTS OF DOSE REDUCTION AND/OR DILUTION ON THE BIOLOGICAL PROPERTIES OF MS CSC FRACTIONS, OR INDIVIDUAL MS COMPONENTS

| Assay | System | MS Entity | n-Fold Dose Reduction, n = | Effect Produced | Reference |
|---|---|---|---|---|---|
| *Skin Painting (SP) Studies* | | | | | |
| SP | SB, m | MS CSC | cont | 10.0 g/yr/m gave 60% PBA | Wynder *et al.* (1957a, 1957b) |
| | | | 1.33 | 7.5 g/yr/m gave 35% PBA | |
| | | | 2 | 5.0 g/yr/m gave 10% PBA | |
| | | | 3.33 | 3.0 g/yr/m gave 0% PBA | |
| SP | SB, m | MS CSC | cont | 50 mg (50%) CSC-acetone gave 45% TBA | Wynder and Hoffmann (1965) |
| | | | 1.5 | 33 mg (33%) CSC-acetone gave 34% TBA | |
| | | | 2.5 | 20 mg (20%) CSC-acetone gave 25% TBA | |
| | | | 5 | 10 mg (10%) CSC-acetone gave 8% TBA | |
| | | | 10 | 5 mg (5%) CSC-acetone gave 2% TBA | |
| SP | SB, m | MS CSC | cont | 25 mg CSC in acetone gave 51% TBA | Gori (1977) |
| | | | 8.3 | 3 mg CSC in acetone gave 2% TBA | |
| SP | SB, m | MS CSC | cont | 25 mg CSC in acetone gave 46% TBA | Gori (1977) |
| | | | 8.3 | 3 mg CSC in acetone gave 1% TBA | |
| SP | SB, m | BaP | cont | 100 μg in acetone gave 85% TBA | Wynder *et al.* (1957) |
| | | | 2 | 50 μg in acetone gave 55% TBA | |
| | | | 20 | 5 μg in acetone gave 0% TBA | |
| | | | cont | 50 μg in acetone gave 55% TBA | Wynder *et al.* (1957) |
| | | | 10 | 5 μg in acetone gave 0% TBA | |
| | | | 50 | 1 μg in acetone gave 0% TBA | |
| *Subcutaneous Injection (SC) Studies* | | | | | |
| SC | m | DBA | cont | 10 μg in solvent gave 11% TBA | Dobrowolskaia-Zavadskaia (1938) |
| | | | 2 | 5 μg in solvent gave 4% TBA | |
| | | | 10 | 1 μg in solvent gave 0% TBA | |
| *Ciliastasis (Cil) Studies* | | | | | |
| Cil | CT, m | $SO_2$ | cont | 300 ppm produced ciliastasis in 90% of the animals in 45 min | Dalhamn (1961) |
| | | | 1.5 | 200 ppm produced ciliastasis in 60% of the animals in 45 min | |
| | | | 3 | 100 ppm produced ciliastasis in none of the animals in 45 min | |
| Cil | CT | CSC Ph | cont | 0.03 g/100 ml produced immediate and complete ciliastasis | Wynder and Hoffmann (1962b, 1963a) |
| | | | 15 | 0.002 g/100 ml produced no ciliastasis | |
| Cil | CT | CSC Ac | cont | 0.04 g/100 ml produced immediate and complete ciliastasis | Wynder and Hoffmann (1962b, 1963a) |
| | | | 6 | 0.007 g/100 ml produced no ciliastasis | |



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Table 28: Continued

| Assay | System | MS Entity | n-Fold Dose Reduction, n = | Effect Produced | Reference |
|---|---|---|---|---|---|
| Cil | CT | CSC Nt | cont | 0.27 g/100 ml produced complete ciliastasis in 10 to 40 min | Wynder and Hoffmann (1962b, 1963a) |
| | | | 8 | 0.034 g/100 ml produced no ciliastasis | |
| Cil | CT | CSC In | cont | 1.10 g/100 ml produced immediate and complete ciliastasis | Wynder and Hoffmann (1962b, 1963a) |
| | | | 20 | 0.055 g/100 ml produced no ciliastasis | |
| Cil | CT | CSC Ba | cont | 1.95 g/100 ml produced immediate and complete ciliastasis | Wynder and Hoffmann (1962b, 1963a) |
| | | | 24 | 0.08 g/100 ml produced no ciliastasis | |
| *Inhalation (Inh) Studies* | | | | | |
| Inh | WB, m | MS | 0 | No human-type carcinoma produced | Aviado (1990) |
| Inh | NO, m | MS | 10 | No human-type carcinoma produced | Aviado (1990) |
| Inh | NO, h | BaP | Footnote[a] | Results on lung tumor production rated "equivocal" by RTECS | Aviado (1990) |
| Inh | NO, m | BaP | Footnote[b] | Results on lung tumor production rated "equivocal" by RTECS | Aviado (1990) |
| Inh | NO, r | DMNA | Footnote[c] | Results on lung tumor production rated "equivocal" by RTECS | Aviado (1990) |
| Inh | NO, m | DMNA | Footnote[c] | Results on lung tumor production rated "equivocal" by RTECS | Aviado (1990) |
| Inh | NO, m | DENA | Footnote[c] | Results on lung tumor production rated "equivocal" by RTECS | Aviado (1990) |

Abbreviations

| | | | |
|---|---|---|---|
| Ac | = acidic fraction | m | = mouse |
| Ba | = basic fraction | MS | = mainstream smoke |
| BaP | = benzo[*a*]pyrene | MS CSC | = mainstream cigarette smoke condensate |
| Cil | = ciliastasis | NO | = nose-only exposure |
| cont | = control | Nt | = neutral fraction |
| CSC | = cigarette smoke condensate | PBA | = papilloma-bearing animals |
| CT | = ciliated tissue | Ph | = phenol fraction |
| DBA | = dibenz[*a,h*]anthracene | r | = rat |
| DENA | = *N*-nitrosodiethylamine | SB | = shaved back |
| DMNA | = *N*-nitrosodimethylamine | $SO_2$ | = sulfur dioxide |
| g | = gram | SP | = skin painting |
| h | = hamster | TBA | = tumor-bearing animals |
| In | = insoluble fraction | WB | = whole-body exposure |
| Inh | = inhalation | yr | = year |

[a] BaP exposure was equivalent to the BaP generated if 135,700 cigarettes were smoked into a 1-$M^3$ space.
[b] BaP exposure was equivalent to the BaP generated if 20 cigarettes were smoked into a 1-$M^3$ space.
[c] *N*-Nitrosamine exposure levels far exceeded those encountered in exposure to ETS.

mice reduced the percent tumor-bearing mice with sarcoma at the site of injection from 11% to 0%. It also showed that 89% of the mice subcutaneously injected with 10 $\mu$g of the potent carcinogen failed to develop sarcoma at the injection site. This is equivalent to the amount of DBA in the MS of 2,500 cigarettes fabricated in 1962 or 1963 (see **Table 4**).

With MS CSC, Wynder *et al.* (1957a, 1957b) showed that a dose reduction from 10.0 to 3.0 g of CSC per mouse per year resulted in no papilloma-bearing mice in the 3.0 g-treated group. This is a 3.3-fold reduction in the dose of skin-painted MS CSC.

Other studies that have revealed the effect of dose reduction on the degree of a biological response include ciliastasis studies in which ciliated tissue was exposed to MS components or MS CSC fractions. Some of these are also summarized in **Table 28**. When dose reductions ranged from a factor of 3 in the case of the sulfur dioxide study to as much as 24 for the MS CSC fractions, the ciliastasis observed at the higher dose was completely nullified by the dose reduction, *e.g.*, a 24-fold reduction of the amount of the CSC basic fraction administered to the ciliated tissue resulted in a reduction from "immediate and complete" ciliastasis to zero ciliastasis. The dose reductions required to nullify the effect of the other CSC fractions are shown in **Table 28**. These range from a factor as low as 6 for the CSC acidic fraction to one as high as 24 for the CSC basic fraction. These dose reductions nullifying the ciliastatic action are much less than the dilutions noted in **Table 26** for the MS components (acrolein and acetone) known to be ciliastatic in *in vitro* systems involving ciliated tissue. The lowest dilutions for MS *vs* ETS are 240 for acetone and 1,500 for acrolein. Both these exceed the dose reductions noted in **Table 28** to completely nullify the ciliastasis of sulfur dioxide and the five CSC fractions.

Thus, the MS components demonstrated to be ciliastatic in *in vitro* systems behave much like CSC or several of its components in the mouse skin-painting studies described previously: At a dose reduction equivalent to about a 25:1 dilution, the ciliastatic activity of MS CSC fractions is reduced from "complete and immediate" to "zero", the tumorigenicity of MS CSC in lifetime skin-painting experiments is reduced from about 50% to 0% in terms of percentage tumor-bearing animals at the termination of the experiment, and the tumorigenicity of several MS CSC PAH components such as BaP or DBA in lifetime skin-painting experiments is similarly reduced from more than 50% to 0%. Each of these findings, in contrast to the view promulgated by agencies such as EPA, suggest that there is indeed a threshold level dose for the agent producing the particular effect under study.

Several MS components listed by OSHA (1994), Hoffmann and Hecht (1990), and EPA (1990b), in addition to being classified as tumorigens, are also known to be ciliastatic when tested in several different *in vitro* systems. However, data are available to show that a substantial amount of these ciliastats in MS, because of their water-solubility, do not traverse the oral cavity to reach the lung, their alleged site of action. It is not unreasonable to assume the same phenomenon occurs with ETS components in the nasal cavity.

Another factor that would have a bearing on the effect of ETS inhaled by a nonsmoker and the differences between MS and ETS is the following: Measurements of MS particulate

matter retention in smokers give retentions ranging from 50 to 90%. Retention of ETS has been estimated as about 11% (*cf.* Hiller *et al.*, 1982a, 1982b; Adlkofer *et al.*, 1989). The lowest dilution factor of 68 calculated for BaP (see **Table 26**) could actually be 4.6 (50/11) to 8.2 (90/11) higher than the value shown, *i.e.*, the dilution factor of 68 for BaP could actually range from 312 (68 x 4.6) to 558 (68 x 8.2). If the % retentions (17 to 41%, depending on the analytical procedure and the subjects' gender) of particulates from *aged and diluted SS* reported by McAughey *et al.* (1994) are used in the calculation, the lowest dilution factor of 68 for BaP would range from 83 to 360. These findings make the dose reduction data and factors shown in **Table 28** even more meaningful.

### *Mutagenesis and Other Studies with ETS*

The early studies on the mutagenicity, particularly as measured in the Ames test with *Salmonella typhimurium*, of MS and MS CSC were reviewed by DeMarini (1983). Little was noted in this publication about the mutagenicity of SS or ETS. The Surgeon General's 1986 report (USPHS, 1987) on involuntary (or passive) smoking included only a brief section on mutagenicity. Urinary mutagenicity, its lack of specificity with regard to MS, and its limitations with regard to its relationship to ETS exposure were discussed as follows:

> Tobacco smoke condensate is strongly mutagenic in bacterial systems (Ames test)... A number of compounds, including polycyclic aromatic hydrocarbons, contribute to this mutagenicity. The urine of cigarette smokers has been found to be mutagenic, and the number of bacterial revertants per test plate is related to the number of cigarettes smoked per day (Yamasaki and Ames, 1977). Urinary mutagenicity disappears within 24 hours after smoking the last cigarette (Kado *et al.*, 1985).
>
> For several reasons, the measurement of mutagenic activity of the urine is not a good quantitative measure of tar absorption... Only a small percentage of what is absorbed is excreted in the urine as mutagenic chemicals... The urine of smokers presumably contains a mixture of many mutagenic compounds. In addition, the test lacks specificity, in that other environmental exposures result in urinary mutagenicity. The test may also be insensitive to very low exposures such as involuntary smoking. However, one study, by Bos and colleagues (1983), indicated slightly increased mutagenic activity in the urine of nonsmokers following tobacco smoke exposure.

### *Effect of ETS Exposure on Nonsmokers*

Since the Surgeon General's 1986 report (USPHS, 1987), the results of several additional studies on urinary mutagenicity and ETS exposure have been published as well as reviews (*cf.* Adlkofer *et al.*, 1989; Eatough *et al.*, 1990a) and critiques (*cf.* Reasor, 1990) of these studies. Several of these studies not only examined the effect of ETS exposure on urinary mutagenicity but also its effect on other factors such as carboxyhemoglobin (COHb) production, nicotine and cotinine levels in body fluids, etc.

**Table 29** summarizes the essence of the experimental procedures used and the results obtained in a number of these laboratory and real-life studies involving measurements of the effects of ETS exposure on the following:

## TABLE 29: MUTAGENESIS AND OTHER STUDIES WITH ETS

| Sample Size | Conditions | Results | Reference |
|---|---|---|---|
| 8 NS | Exposed to ETS generated by 10 smokers in poorly ventilated room .(110 $m^2$, estimated = 275 $m^3$) 6-hr exposure, 157 cigarettes. | Statistically significant enhancement of urinary mutagenicity in passive smokers<br><br>Concentrated air samples from ETS-containing chamber induced about an 11-fold increases in revertants/plate over pre- and post-experiment air samples. | Bos *et al.* (1983) |
| 10 NS | 1. Exposed for 80 min. to SS (not ETS) from 2 to 4 U. Ky. 1R1 reference cigarettes blown into 16 $m^3$ chamber, 6 air changes/hr. | No significant increase in serum nicotine and cotinine; urinary nicotine and cotinine increased; salivary nicotine increased in dose-related manner while in chamber, decreased rapidly after exit. | Hoffmann *et al.* (1984b) |
| 12 NS | 2. Same conditions as in 1. above. | No measurable increase in urinary excretion of *N*-nitrosoproline in NS; urinary excretion of *N*-nitrosoproline did increase in MS-inhaling smokers (previous publication). | |
| INF | 3. Infants exposed at home to ETS. | Increased salivary and urinary nicotine and cotinine. | |
| 392 S<br>472 NS | Exposed to ETS generated by spouse (home) and co-workers (work). | Urinary cotinine of smokers S significantly greater than nonsmokers NS and related to number of cigarettes smoked.<br><br>Urinary cotinine of nonsmokers NS living with smokers S greater than in nonsmokers NS not living with smokers S but not significantly so.<br><br>Urinary cotinine of nonsmokers NS working with smokers S was significantly greater than in nonsmokers NS not working with smokers S.<br><br>Urinary cotinine of nonsmokers NS in urban areas was greater than in nonsmokers NS in rural areas. | Matsukura *et al.* (1984) |
| 100 NS | Comparison of self-reported exposure to levels of biomarkers. | Average cotinine level in nonsmokers NS was 0.3 to 1.0% of that found in active smokers. Dose response matched self-reported ETS exposure for p.m. samples but not for a.m. samples. | Jarvis *et al.* (1984) |

Table 29: Continued

| Sample Size | Conditions | Results | Reference |
|---|---|---|---|
| 3 S<br>3 NS | Exposed to ETS generated by 3 smokers in 12 $m^3$ room; 2 cigt/hr for 5.5 hr; control samples collected after 3-day nonsmoking period for smokers. | Revertants increase in urine from both active and passive smokers. | Einistoe and Sorsa (1985) |
| 6 S | Exposed to ETS generated by 3 smokers in 10 $m^3$ room; air exchange rate = 6.8 times/hr; 3 smokers generated ETS while other 3 breathed ETS, then the two groups switched. | COHb after ETS exposure similar to nonsmoking value; plasma cotinine increased slightly by ETS exposure. | Sorsa *et al.* (1985) |
| 22 S<br>27 NS*<br>20 C | Worked at 3 restaurants for 40 hr/week with "extensive exposure to ETS".<br>Non-exposed nonsmokers | Urinary mutagenicity did not increase significantly due to exposure to ETS and other indoor air factors; levels of PAHs such as BaP were relatively high; air was highly mutagenic; urinary mutagenicity observed in 1 of 17 non-exposed nonsmokers C, 4 of 26 work-exposed nonsmokers NS*, and 12 of 19 smokers S.<br><br>Plasma and urinary cotinine significantly increased in smokers S and work-exposed nonsmokers NS*; values for work-exposed nonsmokers NS* were only 3.5 to 4.1% of those for smokers S. | Husgafvel-Pursiainen *et al.* (1987) |
| 10 NS<br>5 S | Exposed to ETS in unventilated room for 8 hr; ETS from 42 cigarettes smokes by 2 smokers over 8 hr. | Nonsmokers NS showed increased COHb and cotinine but no significant increase in urinary mutagenicity; smokers showed significant increase in urinary mutagenicity. | Scherer *et al.* (1987a, 1987b) |
| | Exposed to ETS in unventilated room for 8 hr; ETS from 100 cigarettes smoked by 5 smokers over 8 hr. | Nonsmokers NS showed increased COHb and cotinine but no significant increase in urinary mutagenicity; smokers S showed significant increase in urinary mutagenicity. | |



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Table 29: Continued

| Sample Size | Conditions | Results | Reference |
|---|---|---|---|
| 10 NS<br>5 NS#<br>10 S | Exposed for 8 hr to ETS generated by 10 smokers so that atmosphere was 10 or 25 ppm in CO. | COHb increased by 0.7 to 2.1% in nonsmokers NS (an increase greater than that usually observed under real-life exposures to ETS); urinary cotinine increased in nonsmokers NS; urinary mutagenicity increased only in smokers S; no difference in biomarkers for nonsmokers exposed to whole ETS (nonsmokers NS) or to ETS VP (masked nonsmokers NS*). | Adlkofer *et al.* (1988) |
| 10 NS<br>10 S | Similar to Scherer *et al.* (1987). | Results essentially same as those reported by Scherer *et al.* (1987). | Scherer *et al.* (1989) |
| 12 NS<br>18 PS<br>7 MOS<br>6 HS | Self-reported ETS exposure. | Sister chromatid exchanges elevated in moderate MOS and heavy smokers HS; no differences between nonsmokers NS and passive smokers PS. | Collman *et al.* (1986) |
| 9 S<br>7 PS<br>7 PS*<br>7 C | Exposed to ETS in indoor restaurants without smoking restrictions | No significant differences between groups/subgroups in sister chromatid exchanges; significant increase in plasma cotinine in ETS-exposed personnel, but level significantly less than that in smokers. | Sorsa *et al.* (1989) |
| ST | By a cellular smoke exposure technique, TA98 *Salmonella typhimurium* exposed to MS from U. Ky. 1R4F cigarettes for 2 hr at a level of 320 mg TPM/$m^3$. | TA98 *Salmonella typhimurium* plus S9 activation system showed a 2-fold increase in the number of revertants/plate. | Bombick *et al.* (1991) |
| WBR | WB rat liver cells exposed to MS from U. Ky. 1R4F cigarettes for 1 or 2 hr at levels from 40 to 640 mg TPM/$m^3$. | Cytotoxicity of 1R4F MS to rat liver cells was concentration and time dependent; no observed effect at 1- and 2-hr exposure at 40 and 160 mg TPM/$m^3$. | |
| ST<br>WBR | *Salmonella typhimurium* and WB rat liver cells exposed to ETS for 3 hr at a level of 1.5 mg TPM/$m^3$; control sample exposed to air for 3 hr. | No difference between air- and ETS-treated samples in this assay. | |

Abbreviations:

| | | | |
|---|---|---|---|
| S | = smoker | MOS | = moderate smoker |
| NS | = nonsmoker | HS | = heavy smoker |
| PS | = passive smoker | WBR | = WB rat liver cells |
| PS* | = passive ex-smoker | NS* | = work-exposed nonsmoker |
| C | = non-exposed nonsmoker | INF | = infants |
| ST | = *Salmonella typhimurium* | | |
| NS# | = nonsmoker wearing particle-trapping mask, thus exposed only to ETS VP | | |

- Mutagenicity of nonsmokers' urine (Adlkofer *et al.*, 1988; Bos *et al.*, 1983; Einistoe and Sorsa, 1985; Husgafvel-Pursiainen *et al.*, 1987; Scherer *et al.* 1987a, 1987b, 1989).

- Nicotine and cotinine levels in nonsmokers' body fluids (serum, urine, saliva) (Adlkofer *et al.*, 1988; Hoffmann *et al.*, 1984b; Jarvis *et al.*, 1984; Matsukura *et al.*, 1984; Husgafvel-Pursiainen *et al.*, 1987; Scherer *et al.*, 1987a, 1987b, 1989); Sorsa *et al.*, 1985, 1989).

- *N*-Nitrosoproline levels in nonsmokers' urine (this study involved SS exposure not ETS exposure) (Hoffmann *et al.*, 1984b).

- Nonsmokers' carboxyhemoglobin (COHb) levels (Adlkofer *et al.*, 1988; Scherer *et al.*, 1987a, 1987b, 1989; Sorsa *et al.*, 1985).

- Several cellular systems (*Salmonella typhimurium*; WB rat liver cells) (Bombick *et al.*, 1991).

- Sister chromatid exchanges in nonsmokers (Collman *et al.*, 1986; Sorsa *et al.*, 1989).

Examination of the findings summarized under ''Results'' in **Table 29** indicates that, in most instances, exposure to ETS produced only minor increases in the factor(s) being measured. The findings, from a diverse set of analyses on ETS-exposed nonsmokers, are those anticipated from the magnitude of the ETS component dilution described by the NAS-NRC (1986) and summarized in **Table 26**.

No significant rise in urinary mutagenicity in ETS-exposed nonsmokers was found in the majority of studies on urinary mutagenicity. The significance of urinary mutagenicity, supposedly caused by exposure of a nonsmoker to ETS and the mutagens contained therein, has been questioned or minimized by several authorities, *e.g.*, Eatough et al. (1990a) wrote in the proceedings of a 1989 conference on ETS:

> Exposure to ETS has also been claimed to result in the excretion of mutagens in the urine of nonsmokers [Bos *et al.*, 1983; Sasson *et al.*, 1985; Scherer *et al.*, 1987b]. This...observation, however, is tentative at present [USPHS, 1987a; NAS, 1986] and is, in any event, of uncertain significance.

and again in 1990, they wrote (Eatough *et al.* 1990b):

> Further studies on the potential use of mutagenicity as a measure of exposure to environmental tobacco smoke are needed. It should be noted that urine mutagenicity cannot be used to assess exposure [NAS, 1986; Sorsa *et al.*, 1985; Sasson *et al.*, 1985; Scherer *et al.*, 1987b] because of the effects of other sources of mutagens, such as diet.

Reasor's comments on the studies on the relationship between ETS exposure and urinary mutagenicity are difficult to improve upon because of their brevity and pertinence (Reasor,

1990). He wrote:

> As a measure of exposure to ETS, studies have been conducted on the ability of concentrated extracts from the urine of nonsmokers to induce mutations in bacteria using the popular Ames assay [Bos *et al.*, 1983; Mohtashamipuri (*sic*) *et al.*, 1987; Putzrath *et al.*, 1981; Scherer *et al.*, 1987a, 1987b; Sorsa *et al.*, 1985]. The rationale behind this approach is that the presence of mutagens in the urine is an indication that the person has been exposed to chemicals that can induce genetic mutations and, theoretically, increase the risk of cancer... [T]o interpret the results of such studies properly, it is necessary to consider certain aspects of the experimental design and analysis that have been employed. In that vein, the following points are significant:
>
> 1. The conditions of exposure to ETS in laboratory settings have not always been realistic in that the levels of ETS have been much higher than commonly encountered under ambient conditions [Bos *et al.*, 1983; Mohtashamipuri (*sic*) *et al.*, 1987].
>
> 2. It is known that diet can markedly influence the mutagenicity of urine [Sasson *et al.*, 1985]. Possible confounding factors such as diet have not always been controlled for in studies examining the mutagenicity of urine following experimental exposure to ETS [Bos *et al.*, 1983].
>
> 3. Claims of increased urinary mutagenicity have not always been supported by the data because of the absence of statistical analysis [Mohtashamipuri (*sic*) *et al.*, 1987; Sorsa *et al.*, 1985] or because of misrepresentation of the actual data presented [Sorsa *et al.*, 1985].
>
> 4. The putative urinary mutagens have not been identified.
>
> 5. The biological significance of low-level mutagencity (*sic*) in urinary concentrates has not been established.

Reasor concluded:

> When studies in this area are considered together, there is no compelling evidence that exposure to ETS results in an increase in urinary mutagenicity or that it will be possible to assess exposure to ETS by its use.

Nicotine and cotinine have been detected in body fluids of nonsmokers exposed to ETS, but most of the studies show only slight increases over the levels of these two compounds in the body fluids of nonsmokers not exposed to ETS. In most instances, the investigators have rated the increase in nicotine and cotinine levels as not significant.

Data reported by Jarvis *et al.* (1984) on nicotine and cotinine in body fluids of smokers and nonsmokers exposed and not exposed to ETS are summarized in **Table 30.**

Because of the long half-life of cotinine relative to that of nicotine, the cotinine data are more meaningful than the nicotine data. The results of the cotinine-in-urine measurements are particularly interesting. Cotinine in smokers' urine averaged more than 180 times the average

TABLE 30: NICOTINE AND COTININE IN BODY FLUIDS OF SMOKERS AND NONSMOKERS EXPOSED AND NOT EXPOSED TO ETS

| | Nicotine, ng/ml | | Cotinine, ng/ml | | |
|---|---|---|---|---|---|
| Group | Plasma | Urine | Plasma | Urine | Saliva |
| Nonsmokers, Not Exposed | 1.04 | 3.87 | 0.82 | 1.55 | 0.73 |
| Nonsmokers, Exposed | 0.77 | 12.11 | 2.04 | 7.71 | 2.48 |
| Smokers | 14.80 | 1759.9 | 275.2 | 1391.0 | 309.9 |

for ETS-exposed nonsmokers (1391/7.71) and about 900 times the average for non-exposed nonsmokers (1391/1.55).

However, one cannot and should not conclude from these data that the amount of ETS retained by passive smokers is about one two-hundredths of that retained by active smokers. The fundamental quantitative and phase-related differences between MS and ETS preclude such a conclusion: As noted previously (Rodgman, 1991, 1992), nicotine in MS is protonated and is primarily (> 99.9%) a particulate-phase component; nicotine in SS and ETS is nonprotonated and in ETS is primarily (> 95%) a vapor-phase component. Thus, nicotine uptake from ETS, as measured by nicotine and cotinine levels in body fluids, does not provide a measure of ETS particulate matter uptake.

The magnitude of the nicotine uptake from ETS that resulted in the low levels of nicotine and cotinine in the nonsmokers' body fluids is not considered to represent a toxicological problem to the ETS-exposed nonsmoker (Matsukura *et al.*, 1984).

The slight increases observed in the carboxyhemoglobin levels of ETS-exposed nonsmokers (see summary of such studies in **Table 29**) due to the carbon monoxide content of ETS are also not considered to represent a significant toxicological problem to the ETS-exposed nonsmoker. The effects on smokers of the exposure to the levels of carbon monoxide in MS and the effects on nonsmokers of exposure to the levels of carbon monoxide in ETS were discussed in detail by Wakeham (1976, 1977). Reiterating his 1976 comments, Wakeham stated in 1977:

> [C]igarette smoking is an insignificant source of carbon monoxide in the overall atmosphere as compared with other man-made sources. Even in tightly closed spaces with a large percentage of smokers, only rarely is it possible to build up concentrations which would exceed the established threshold limiting values for extended exposures...carboxyhemoglobin levels in nonsmokers resulting from carbon monoxide in environmental tobacco smoke are below the amount needed to produce the maximum allowable limit of 4% carboxyhemoglobin in the blood...No strong evidence has been found indicating adverse effects in healthy individuals from concentrations of carboxyhemoglobin at or below these levels.

In an attempt to put the results of the studies described in **Table 29** in perspective, the major findings from these studies are summarized in capsule form in **Table 31**. In general, ETS exposure has little effect on the various systems and factors studied.

**TABLE 31: EFFECTS OF ETS EXPOSURE ON VARIOUS SYSTEMS**

| System | Results[a] | Reference |
|---|---|---|
| Urinary mutagenicity | significant increase[b] | Bos *et al.* (1983) |
| | increase | Einistoe *et al.* (1985) |
| | slight increase | Sorsa *et al.* (1985) |
| | increase but not significant | Husgafvel-Pursiainen *et al.* (1987); Scherer *et al.* (1987a, 1989); Adlkofer *et al.* (1988) |
| Nicotine/cotinine | | |
| In serum | no significant increase[c] | Hoffmann *et al.* (1984) |
| | significant increase but cotinine level less than in smokers[b] | Sorsa *et al.* (1989) |
| In urine | increase[c] | Hoffmann *et al.* (1984) |
| | increase but not significant | Matsukura *et al.* (1984) |
| | 0.30 to 1.0% of level found in smokers | Jarvis *et al.* (1984) |
| | slight increase | Adlkofer *et al.* (1988); Scherer *et al.* (1987a, 1989) |
| In saliva | increase proportional to dose[c] | Hoffmann *et al.* (1984) |
| Carboxyhemoglobin | COHb value similar to that observed in nonsmokers | Sorsa *et al.* (1985) |
| | slight increase in COHb | Scherer *et al.* (1987a, 1989) |
| | COHb increase of 0.7 to 2.1% | Adlkofer *et al.* (1988) |
| Sister chromatid exchange | no difference between nonsmokers and passive smokers | Sorsa *et al.* (1989); Collman *et al.* (1986) |
| *Salmonella typhimurium* + WB rat liver cells | no difference between ETS- and air-exposed Salmonella | Bombick *et al.* (1991) |

[a] See **Table 29** for more detailed description.
[b] See criticisms by Reasor (1990).
[c] Study involved SS not ETS exposure.

*Inhibitors and Anticarcinogens in Tobacco Smoke (MS, SS, and ETS)*

In hundreds of publications over the years, those opposed to tobacco smoking, particularly cigarette smoking, have discussed certain smoke components in terms of their adverse effect in a variety of bioassays, *e.g.*, any MS component previously demonstrated to be tumorigenic to the skin of a susceptible strain of mice painted daily with massive doses of the component is described (and many times defined) as a ''tumorigenic'' or ''carcinogenic'' component of MS. However, the specific components under discussion are present in MS at levels at which they have never been shown to be ''tumorigenic'' or ''carcinogenic'' in any species or strain of laboratory animal. Some of the authors have even noted that a certain MS component is present in MS at a level insufficient to cause the biological effect observed or there are insufficient data available to define the role of the component in tobacco carcinogenesis. These statements are made despite the fact that, sometimes in the same publication (or in another publication), the component is described as ''tumorigenic'' with the implication that it is ''tumorigenic'' to the active smoker. Examples of these statements are provided in **Table 4**.

The proponents of the adverse effect of cigarette smoke and some of its components, such as those described as ''tumorigenic'' in the two ''Lists of 43'' (**Table 4**), rarely discuss the details of the experiments in which the specific component was initially demonstrated to be tumorigenic. They also seldom discuss the fact that cigarette MS (or SS) contains numerous components that have been demonstrated, in the same types of bioassays used to demonstrate the ''tumorigenicity'' of components in the ''Lists of 43,'' to be inhibitors of the tumorigenicity of ''tumorigenic'' MS components or to be anticarcinogens that offset or nullify the ''tumorigenicity'' of one or more of the listed ''tumorigenic'' MS components.

Inhibitors of carcinogens, or anticarcinogens, are agents which prevent the development of cancer. Wattenberg (1975) classified them in three categories based on the time in the carcinogenic process when they are effective. The first category consists of chemicals that prevent the formation of carcinogens (or tumorigens) from precursor substances. Examples of this group of inhibitors are ascorbic acid (Mirvish, 1981a, 1981b), tocopherols (Newmark and Mergens, 1981), and phenols (Newmark and Mergens, 1981; Kuenzi *et al.*, 1984) which inhibit the formation of nitroso carcinogens from precursor amine and nitrite both *in vivo* and *in vitro*. The second category comprises ''blocking agents'' which inhibit carcinogenesis by preventing carcinogenic compounds from reaching or reacting with critical target sites in the tissues. An example of this group is disulfiram (Wattenberg, 1975) which inhibits the metabolism of symmetrical dimethylhydrazine to its carcinogenic metabolites (Fiala *et al.*, 1977). The inhibitors in the last category are called ''suppressing agents.'' They function by suppressing the expression of neoplasia in cells exposed to a carcinogenic agent. An example of this group of anticarcinogens is the retinoids, *i.e.*, Vitamin A and related compounds (*cf.* Slaga and DiGiovanni, 1984).

Despite the fact that the anticarcinogenicity of certain components of tobacco (Falk *et al.*, 1964) and tobacco smoke (Hoffman and Griffin, 1958; Homburger and Treger, 1965) and of tobacco smoke itself (Homburger *et al.*, 1968) has been known for over four decades, most of the discussion over the years has been directed at the smoke components alleged to be tumorigenic to the smoker rather than at the smoke components reported to possess anticarcinogenic properties.

In their 1964 review on tobacco carcinogenesis, Wynder and Hoffmann briefly discussed the possibility of anticarcinogenic agents in tobacco smoke:

> Thought must be given to possible antitumorigenic agents both in terms of ''antiinitiators'' as well as ''tumor retarders.'' The former fits into the general concept of competitive carcinogenesis between strong and weak PAH as well demonstrated in studies by Steiner and Falk (1951) and...by Kotin and Falk (1963), using subcutaneous tissues as test tissue and with our own studies (Wynder and Hoffmann, 1962b, [1963d]) with epithelial tissue. Of particular interest is the inhibiting effect of benz[*a*]anthracene to B[*a*]P.
>
> ...[T]he effect on mouse skin of two representatives of the tobacco smoke paraffins ($n$-$C_{31}H_{64}$ and $n$-$C_{35}H_{72}$) was...a significant ''inhibiting'' effect on the tumorigenicity of B[*a*]P.

Again in their 1967 book, Wynder and Hoffmann (1967) discussed possible anticarcinogenic components of tobacco smoke as follows:

> *Any discussion of as complex a carcinogen as tobacco smoke should at least mention the existence of anticarcinogens...* Experiments with subcutaneous injections, as conducted by Steiner and Falk (1951), have clearly demonstrated that a weak carcinogen such as benz[*a*]anthracene can reduce the effect of a potent carcinogen such as BaP. In similar experiments using mouse skin as test organ, Hoffmann and Wynder[1] showed that benz[*a*]anthracene may also reduce the activity of BaP in this setting. Whether this interaction applies to a similar extent when the substances are contained in an admixture such as tobacco ''tar'' requires separate investigations. In one such study, painting mice with a dilute solution of benz[*a*]anthracene in addition to tobacco ''tar,'' or adding this component to tobacco ''tar'' did not significantly alter the tumorigenic activity of the ''tar''[1]...
>
> [1] Citation is to unpublished research findings.
>
> The principle of anticarcinogens in the sense of ''competitive'' effect on tissue constituents may also apply to phenols... Paraffins represent an example of components that may interfere with the absorption of carcinogens [as shown] by Hoffmann and Wynder [1962]... [T]hese interactions are readily demonstrable when testing two different components, but they may be less clear-cut when evaluated as part of a ''tar'' mixture. The existence of anticarcinogens, however, must be considered in evaluating any complex mixture such as tobacco smoke condensate.
>
> Several investigators have noticed some inhibition of tumor growth by tobacco smoke condensate...[including] Hoffman and Griffin (1958)...Falk *et al.* (1964)...[and] Homburger and Tregier [*sic*] (1960)... [I]t should not come as a surprise that a material which has been proved to be carcinogenic may also interfere with tumor development, if not with tumor initiation...
>
> An explanation of the tumorigenic activity of tobacco smoke condensate in terms of single

constituents is made more difficult by the presence of substances that may act as anticarcinogens and/or absorption retarders, especially for tumorigenic agents. It is known that structurally related noncarcinogenic hydrocarbons can inhibit the effect of carcinogenic hydrocarbons. The same interrelationship may apply to tumor-promoting and nontumor-promoting phenols. (*Emphasis added:* AR)

Thus, investigators opposed to tobacco smoking readily accept the following:

- The findings in studies with laboratory animals treated with a simple system comprising *Tumorigen A* and *Tumorigen B* where the data indicated that the two tumorigens exert an additive effect in tumor production.

- The findings in studies with laboratory animals treated with a simple system comprising *Tumorigen A* and *Nontumorigen C* where the data indicated that the nontumorigen, when present in an appropriate amount relative to *Tumorigen A*, completely or partially offset the effect of the tumorigen, *i.e.*, *Nontumorigen C* exerted an antitumorigenic effect.

- The premise that *Tumorigen A* and *Tumorigen B* will behave additively in the production of tumors in laboratory animals treated with a complex mixture, *e.g*, CSC, raw and cooked foods, containing *Tumorigen A* and *Tumorigen B*.

- The premise that *Nontumorigen C* will offset the effect of *Tumorigen A* in laboratory animals treated with a complex mixture, *e.g*, raw or cooked foods, engine exhausts, containing *Tumorigen A* and *Nontumorigen C* [*cf.* Grasso (1984); Slaga and DiGiovanni (1984)].

However, the opponents of tobacco smoking apparently view tobacco smoke as a complex mixture entirely different from other complex mixtures such as raw or cooked foods, engine exhausts, etc. They do not accept the premise that *Nontumorigen C* will offset the tumorigenic effect of *Tumorigen A* in laboratory animals treated with the complex mixtures CSC, MS, SS, or ETS containing *Tumorigen A* and *Nontumorigen C* (Hoffmann *et al.*, 1993).

One of the early examples of MS components inhibiting the action of a ''tumorigen'' on the ''Lists of 43'' was described in the early 1960s by Wynder and Hoffmann (1961a). This finding was an outgrowth of investigations on the effect of organic solvent extraction of tobacco on the PAH content of the extracted tobacco smoke. Proposed precursors in tobacco of PAHs in cigarette MS were the saturated aliphatic hydrocarbons (Lam, 1955; Wynder, 1956), the phytosterols (Wright, 1957b; Wynder *et al.*, 1958a, 1958b, 1959), and terpenoid compounds other than the phytosterols (Wright, 1957b). These compounds are removable almost totally or to a substantial degree by extraction of tobacco with organic solvents such as hexane or pentane. Cigarettes fabricated from the extracted tobacco yielded lower quantities in MS of PAHs such as BaP and DBA that were known under certain laboratory conditions to produce tumors on the shaved backs of susceptible strains of mice. Skin-painting studies with MS CSC collected by smoking cigarettes made with the control and extracted tobaccos gave a lower percentage of

tumor-bearing animals (TBA) in the extracted tobacco CSC group. However, the decrease in % TBA was much less than the percent decrease in the level in the CSC of tumorigenic PAHs such as BaP (Wynder, 1956; Wright, 1957b; Wynder *et al.*, 1958a, 1958b, 1959; Wynder and Hoffmann, 1959a, 1959b).

One explanation for this difference was that the solvent extracted almost all the aliphatic saturated hydrocarbons from the tobacco, and thus, they did not appear in the MS from the extracted-tobacco cigarettes. Wynder and Hoffmann (1961a, 1962b) and Hoffmann and Wynder (1962) reported that this aliphatic saturated hydrocarbon fraction (constituting about 3% of the MS CSC) inhibited the carcinogenicity of PAHs, including BaP. The components in the aliphatic hydrocarbon fraction ranged from pentadecane ($C_{15}H_{32}$) to pentatriacontane ($C_{35}H_{72}$). Each hydrocarbon was present as the *normal*, *iso*, and *anteiso* isomers. The $C_{27}$ to $C_{33}$ hydrocarbons constituted about 80% of the saturated hydrocarbon fraction; $C_{31}$ (*n*-hentriacontane) and $C_{33}$ (*n*-tritriacontane) hydrocarbons are the most plentiful components. Subsequent study with improved analytical methodology demonstrated the presence of trace amounts of isomeric aliphatic saturated hydrocarbons with as many as 40 carbons.

Mouse skin-painting studies with BaP and the saturated hydrocarbons (SHC) *n*-hentriacontane ($C_{31}H_{64}$) and *n*-pentatriacontane ($C_{35}H_{72}$, where the SHC:BaP ratio was 200:1 and 100:1, showed that both hydrocarbons exerted a significant inhibiting effect at both levels on the tumorigenicity of BaP to mouse skin (Wynder and Hoffmann, 1961a, 1962b; Hoffmann and Wynder, 1962).

When the saturated hydrocarbon content (usually about 3%) of CSC was increased from 3% to 4% (a 33% increase) by addition of the saturated hydrocarbon fraction isolated from CSC, the tumorigenicity of the CSC decreased: The percent TBA decreased from 40% to 24%. The MS of a cigarette delivering 20 mg of CSC contains about 0.6 mg (600,000 ng) of this hydrocarbon fraction and 10 ng of BaP, a saturated hydrocarbon fraction:BaP ratio of 60,000:1, far in excess of the 200:1 or 100:1 ratio that produced the significant inhibition of the tumorigenicity of BaP (Wynder and Hoffmann, 1962b, 1964, 1967).

Early studies on the anticarcinogenic properties of tobacco smoke and CSC included those of Homburger (Homburger, 1965; Homburger and Treger, 1965; Homburger *et al.* (1968).

Other MS components may have also influenced the PAH and mouse skin-painting results obtained with control tobacco CSC and extracted tobacco CSC. The extraction of tobacco with a solvent such as hexane not only removed the saturated aliphatic hydrocarbon inhibitors from the tobacco, thus making impossible their transfer to MS when such tobacco is smoked, but also removed substantial amounts of other tobacco components such as β-sitosterol (Wynder *et al.*, 1959), α-tocopherol (Vitamin E) (Rowland, 1958; Rodgman and Cook, 1960), indole (Rodgman and Cook, 1962), α- and β-4,8,13-duvane-1,3-diol (Roberts and Rowland, 1962; Rowland *et al.*, 1964; Saito *et al.*, 1985), and *D*-limonene, thus eliminating or drastically reducing the amount transferred to MS during the smoking process. Subsequently, it was demonstrated:

- These tobacco components were transferred from tobacco to MS during the smoking process and to SS during cigarette smolder between puffs and/or, in some cases, were generated during the smoking process, *e.g.*, indole.

- These compounds were anticarcinogenic against several of the ''tumorigens'' in the ''Lists of 43,'' *e.g.*, PAHs, NNAs, ethyl carbamate.

Neither the identity of several of these tobacco and smoke components (MS or SS) nor their anticarcinogenicity was known in the late 1950s/early 1960s.

Comparison of the list of the 4,800 or so identified components in tobacco smoke with lists (Fay *et al.*, 1984; Slaga and DiGiovanni, 1984) of compounds shown to possess inhibitory or anticarcinogenic action in carcinogenesis-type experiments in laboratory animals reveals not only that tobacco smoke contains numerous anticarcinogens but also that the levels in smoke of many of them far exceed those of the ''tumorigens'' listed by Hoffmann and Hecht (1990) and OSHA (1994) (see **Table 4**).

A few of the inhibitory and anticarcinogenic MS components were discussed previously, but these represent only a small fraction of the identified MS components which have been shown to possess one or the other of these properties. Slaga and DiGiovanni (1984) reviewed the studies in which many compounds were demonstrated to be anticarcinogenic. From their review and other publications (Fay *et al.*, 1984), a list of MS components demonstrated to be inhibitors and anticarcinogens to the components in the ''Lists of 43'' was compiled and is shown in **Table 32**.

From the data presented in **Table 4** on the per cigarette MS delivery, it may be calculated that the PAHs included by Hoffmann and Hecht (1990) and OSHA (1994) on the ''Lists of 43'' contribute from about 4 to 10 $\mu$g/g of MS CSC. Nontumorigenic PAH components of MS, such as naphthalene, anthracene, phenanthrene, fluoranthene, pyrene, benzo[*e*]pyrene, and benzo[*b*]triphenylene total 90 to 180 $\mu$g/g of CSC. The anticarcinogenic effect of nontumorigenic PAHs and weakly tumorigenic or nontumorigenic aza-arenes against carcinogenic PAHs has been known since the mid-1940s (*cf.* Lacassagne *et al.*, 1945; Steiner and Falk, 1951; Slaga and DiGiovanni, 1984). The PAH distribution from a variety of environmental sources and from a variety of cooked foodstuffs was studied in attempts to correlate the results of biological studies with the PAHs present. Logically, this same type of study was eventually applied to the PAHs present in cigarette smoke.

**TABLE 32: INHIBITORS AND ANTICARCINOGENS IN TOBACCO SMOKE**

| Component | Approximate Delivery, μg/g MS CSC | Effective Against | References |
|---|---|---|---|
| Total of "tumorigenic" PAHs in the "Lists of 43" | 4 - 10 | | |
| saturated aliphatic hydrocarbons[a] [*e.g.*, $C_{31}H_{64}$] | 30,000 | BaP | Wynder and Hoffmann (1962b) |
| *D*-limonene | 15 - 50 | NNK<br>DB[*a,i*]P | Wattenberg and Coccia (1991)<br>Homburger *et al.* (1971) |
| benzene | 480 - 1,900 | BaP, DBA | Crabtree (1946, 1947) |
| naphthalene | 80 - 160 | BaP, DBA | Crabtree (1946, 1947) |
| anthracene | 4 - 7 | BaP, DBA | Crabtree (1946, 1947) |
| phenanthrene | 2 - 4 | DMBA | DiGiovanni *et al.* (1980) |
| fluoranthene | 3 - 4 | DMBA | DiGiovanni *et al.* (1980)<br>Slaga *et al.* (1979) |
| pyrene | 3 - 4 | DMBA | DiGiovanni *et al.* (1980)<br>Slaga *et al.* (1979) |
| benzo[*e*]pyrene | 0.2 | DMBA | DiGiovanni *et al.* (1980)<br>Slaga *et al.* (1979) |
| benzo[*b*]triphenylene [b] | 0.05 | MC, DBA, DMBA | Slaga and Boutwell (1977); Slaga *et al.* (1978) |
| 2*H*-1-benzopyran-2-one [*coumarin*] | | BaP, DMBA | Wattenberg *et al.* (1979) |
| 2-propenoic acid, 3-(3,4-dihydroxyphenyl)- [*caffeic acid*] | | | Wattenberg (1981) |
| 2-propenoic acid, 3-(3-hydroxy-4-methoxyphenyl)- [*ferulic acid*] | | | Wattenberg (1981) |
| 3*H*-2-furanone, dihydro-5-methyl- [*α-angelica lactone*] | | BaP | Wattenberg *et al.* (1979) |
| β-sitosterol | 1,200-1,600 | NNA<br>PAH | Wattenberg (1981)<br>Yasukawa *et al.* (1991) |
| cholesterol | 400 - 800 | NNA | Cohen *et al.* (1982) |
| α-tocopherol [*Vitamin E*] | 400 - 600 | MC, DMBA<br>DB[*a,i*]P<br>1,2-DMH | Shamberger (1970); Shklar (1982); Slaga and Bracken (1977); Viaje *et al.* (1977); Weerapradist and Shklar (1982); Mirvish (1986); Epstein *et al.* (1967); Toth and Patil (1983) |
| | | CSC | Rosin (1982) |

Table 32: Continued

| Component | Approximate Delivery, μg/g MS CSC | Effective Against | References |
|---|---|---|---|
| indole | 400 - 600 | NNA | Matsumoto *et al.* (1977) |
| indole-3-acetonitrile | . | BaP | Kovacs and Somogyi (1970) |
| dibenz[*a*,*h*]acridine[c] | | DBA | Lacassagne *et al.* (1945) |
| α-4,8,13-cyclodecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)- [*α-4,8,13-duvane-1,3-diol*] | 8 - 20 | DMBA | Saito *et al.* (1985) |
| β-4,8,13-cyclodecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)- [*β-4,8,13-duvane-1,3-diol*] | 12 - 25 | DMBA | Saito *et al.* (1985) |
| cinnamic acid, 3,4-dihydroxy- | | BaP | Wattenberg *et al.* (1980) |
| cinnamic acid, 2-hydroxy- | | BaP | Wattenberg *et al.* (1980) |
| phenol, 4-methoxy- | | BaP | Wattenberg *et al.* (1980) |
| benzoic acid, 3,4,5-trihydroxy- [*gallic acid*] | | NNA | Mirvish *et al.* (1975) |
| 1*H*-purine-2,6-dione,3,7-dihydro-3,7-dimethyl- [*theobromine*] | | EC | Nomura (1983) |
| 1*H*-purine-2,6-dione,3,7-dihydro-1,3,7-trimethyl- [ *caffeine*] | | EC<br>DMB<br>NNA | Nomura (1983); Perchellet and Boutwell (1981); Mirvish *et al.* (1975) |
| maleic anhydride | | PAH<br>DMBA | Klein (1965); Slaga *et al.* (1983) |
| 1-propene-1,2,3-tricarboxylic acid [*aconitic acid*] | | BaP | Kallistratos (1975); Kallistratos and Fasske (1976) |
| ethanol | | NNN | Waddell and Marlow (1983) |
| *n*-butanol | | NNN | Waddell and Marlow (1983) |
| *tert*-butanol | | NNN | Waddell and Marlow (1983) |
| carbon disulfide | | 1,2-DMH | Wattenberg and Fiala (1978) |
| selenium | | DMBA | Shamberger (1970) |

Table 32: Continued

| Component | | Approximate Delivery, $\mu g/g$ MS CSC | Effective Against | References |
|---|---|---|---|---|
| Abbreviations | | | | |
| MC | = | 3-methylcholanthrene; correct name is 1,2-dihydro-3-methylbenz[*a*]aceanthrylene | | |
| DB[*a,i*]P | = | dibenzo[*a,i*]pyrene; correct name is benzo[*rst*]pentaphene | | |
| PAH | = | polycyclic aromatic hydrocarbon | | |
| DBA | = | dibenz[*a,h*]anthracene | | |
| DMBA | = | 7,12-dimethylbenz[*a*]anthracene | | |
| 1,2-DMH | = | 1,2-dimethylhydrazine | | |
| NNA | = | nitrosamine | | |
| EC | = | ethyl carbamate | | |

[a] This fraction consists primarily of the *normal-*, *iso-* (2-methyl-), and *anteiso-* (3-methyl-) alkanes from $C_{15}$ to $C_{40}$, a total of at least 78 different saturated hydrocarbons, *e.g.*, the $C_{15}$ isomers present are *n*-pentadecane, *iso*-pentadecane (2-methyltetradecane), and *anteiso*-pentadecane (3-methyltetradecane).

[b] Benzo[*b*]triphenylene was formerly named dibenz[*a,c*]anthracene.

[c] See discussion pertinent to **Table 12**.

In 1962, Wynder and Hoffmann compared the carcinogenicities of gasoline engine exhaust ''tar'' and CSC in mouse skin-painting paintings. They also estimated the amounts of PAHs in the two test materials. Their data indicated that the engine exhaust ''tar'':CSC ratio for individual PAHs was extremely high not only for several of the ''tumorigenic'' PAHs listed in **Table 4** but also for the noncarcinogenic (and anticarcinogenic) PAHs such as pyrene, fluoranthene, and benzo[*e*]pyrene. The ratios for the individual PAHs are shown in **Table 33**. Despite the tremendous differences in the ratios of ''tumorigenic'' PAHs, the percentage of tumor-bearing animals in the engine exhaust ''tar''-treated group was slightly less than 3 times (54% *vs* 20% carcinoma-bearing animals) that in the CSC-treated group when both groups were painted with equal volumes of 33% exhaust ''tar'' or CSC in acetone for 18 months. Dose reduction to 25% solutions gave a 6-fold difference (48% *vs* 8%). When painted with 10% solutions, the exhaust ''tar''-treated group showed 32% tumor-bearing animals, the CSC-treated group showed 0% (Wynder and Hoffmann, 1962a).

After noting that

> [L]aboratory findings as presented in this report cannot be directly applied to man...[J]ust because the condensates used in this study produced skin cancer in experimental animals under the conditions described does not prove that they will produce cancer in man

they acknowledged the possible efficacy of the saturated hydrocarbons (paraffins) (*cf.* Wynder and Hoffmann, 1962b, 1964, 1967) and noncarcinogenic PAHs as anticarcinogens:

> [I]t was anticipated that the...exhaust gas ''tar'' would be many times more active than tobacco smoke condensate. However, as shown, it is only approximately twice as active. This relatively small increase in biological activity of...exhaust gas ''tar'' raises the question of possible anticarcinogenic factors that may be more prevalent in engine exhaust ''tar''... [O]ne may theorize

**TABLE 33: RATIOS FOR INDIVIDUAL POLYCYCLIC AROMATIC HYDROCARBONS IN GASOLINE ENGINE EXHAUST "TAR" (EET) AND CIGARETTE SMOKE CONDENSATE (CSC)**

| Polycyclic Aromatic Hydrocarbon | Ratio $PAH_{EET}:PAH_{CSC}$ |
|---|---|
| pyrene | 500:1 to 700:1 |
| fluoranthene | 275:1 to 390:1 |
| chrysene | 87:1 to 115:1 |
| alkylchrysenes[a] | 33:1 to 45:1 |
| benz[*a*]anthracene (BaA) | 600:1 |
| benzo[*b*]fluoranthene[b] | 640:1 |
| benzo[*j*]fluoranthene | 85:1 to 110:1 |
| benzo[*k*]fluoranthene | 200:1 to 360:1 |
| dibenz[*a,h*]anthracene (DBA) | 17:1 to 25:1 |
| benzo[*a*]pyrene (BaP) | 45:1 |
| benzo[*e*]pyrene | 4200:1 |
| indeno[1,2,3-*cd*]pyrene | >80:1 |

[a] Similar to 5-methylchrysene
[b] Current name is benz[*e*]acephenanthrylene

that some of the noncarcinogenic polynuclear hydrocarbons that are present in engine exhaust gas "tar" in far greater concentrations than in tobacco smoke condensate may interfere with the resorption of the "tar." Some of the oily materials in gasoline engine exhaust "tar" and the paraffins in tobacco smoke condensate may also act as anticarcinogens.

Because of their low vapor pressures, many of the allegedly potent "tumorigens" (and initiators) such as the PAHs (BaP, DBA, etc.) and the aza-arenes (dibenz[*a,h*]acridine, etc.) are found in the particulate phase, *i.e.*, in the aerosol particle, of MS, SS, and ETS. For the same reason, many of the demonstrated anticarcinogens and inhibitors listed in **Table 32** are found in the aerosol particles, *e.g.*, the saturated aliphatic hydrocarbons, typified by *n*-hentriacontane (Eatough *et al.*, 1990a); β-sitosterol and cholesterol (Eatough *et al.*, 1990a); α-tocopherol; indole and indole-3-acetonitrile; the duvatrienediols; tricyclic PAHs (anthracene, phenanthrene), tetracyclic PAHs (pyrene, fluoranthene), and pentacyclic PAHs (benzo[*e*]pyrene). Unlike basic smoke components such as nicotine which are almost totally in the MS particles ($pH < 7.0$) but virtually absent from ETS particles ($pH > 7.0$), the bulk of each of the components just discussed remains in the aerosol particles: They do not transfer to the ETS vapor phase by evaporative processes. Thus, the anticarcinogens and inhibitors are always in close proximity to the "tumorigens" in the aerosol particles and are able to exert their anticarcinogenic or inhibitory effect.

Just as there are many compounds known to be inhibitory or anticarcinogenic to the action of compounds which produce tumors in a variety of laboratory animals, so there are many compounds known to be antimutagenic to compounds which show mutagenicity in various

bacterial systems, *e.g.*, *Salmonella typhimurium* in the Ames test. Some of the antimutagens are also anticarcinogens.

In their review on antimutagens and inhibitors of mutagenesis, Ramel *et al.* (1986) discussed the many antimutagens found naturally occurring in plants, particularly edible plants. They did not discuss tobacco specifically, but they did discuss the natural occurrence in plants of the following compounds known to be antimutagens: α-tocopherol, 2*H*-1-benzopyran-2-one (coumarin), 7-hydroxy-2*H*-1-benzopyran-2-one (umbelliferone), and 3-phenyl-2-propenal (cinnamaldehyde). All four have been identified in tobacco; all but 7-hydroxy-2*H*-1-benzopyran-2-one have been identified in tobacco smoke.

Lee and Reed (1983) investigated the possible antimutagenic activity of nicotine vs NDMA and nicotine *vs* BaP in the Ames test (*Salmonella typhimurium* TA 100). They observed that nicotine inhibits the mutagenic activity of the NDMA but not BaP. Although the mechanism(s) of this antimutagenesis are not elucidated, the recent report (Murphy and Heilblum, 1990) on the inhibition of metabolism of the TSNA NNN by nicotine suggests nicotine inhibition of NNA activation may be involved. Recently, Lee and Fulp (1991) repeated the earlier experiment and confirmed the antimutagenic effect of nicotine on NDMA.

In another study, Lee *et al.*, (1991, 1994) observed that CSC inhibits the mutagenic activity of several aza-arenes when tested in the Ames assay with *Salmonella typhimurium* TA 98 in the presence of S9 activation system. The mutagenic heterocyclic amines tested included:

- Glu-P-1 2-amino-6-methyl-dipyrido[1,2-*a*:3',2'-*d*]imidazole
- Glu-P-2 2-amino-dipyrido[1,2-*a*:3',2'-*d*]imidazole
- IQ 2-amino-3-methyl-imidazo[4,5-*f*]quinoline
- MeIQ 2-amino-3,4-dimethyl-imidazo[4,5-*f*]quinoline
- Trp-P-1 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole
- Trp-P-2 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole.

These compounds, known as cooked food mutagens, are some of the most potent bacterial mutagens known (Sugimura *et al.*, 1977; Yamamota *et al.*, 1978; Yamashita *et al.*, 1985, 1986). The mutagenicities of these six compounds and CSC in the Ames assay with *Salmonella typhimurium* TA 98 and TA 100 are listed in **Table 34**. Several have been reported to be carcinogenic in experiments with laboratory animals (Felton and Knize, 1990).

TABLE 34: MUTAGENIC ACTIVITIES OF "COOKED FOOD" MUTAGENS TOWARDS *Salmonella typhimurium*[a]

| | Mutagenic Activity, revertants/$\mu$g | | | |
|---|---|---|---|---|
| | TA98 | | TA100 | |
| Compound (Designation) | Lee *et al.* (1994) | Sugimura (1986) | Lee *et al.* (1994) | Sugimura (1986) |
| 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ)[b] | 222,000 | 433,000 | 11,000 | 7,000 |
| 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ) | 1,327,000 | 661,000 | 70,000 | 30,000 |
| 2-amino-6-methyldipyrido[1,2-*a*:3',2'-*d*]imidazole (Glu-P-1) | 73,000 | 49,000 | 4,000 | 3,200 |
| 2-aminodipyrido[1,2-*a*:3',2'-*d*]imidazole (Glu-P-2) | 600 | 1,900 | 400 | 1,200 |
| 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-1)[b] | 20,000 | 39,000 | 500 | 1,700 |
| 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-2)[b] | 103,000 | 104,200 | 2,000 | 1,800 |
| CSC | 2 | | 1 | |

[a] Tests with *Salmonella typhimurium* involved use of S-9 mix.
[b] Identified in tobacco smoke.

In possibly the first demonstration of the biological activity of the antimutagens in tobacco smoke, Lee *et al.* (1994) reported that 50 to 100 $\mu$g of CSC per plate suppressed the mutagenic activity of these compounds by as much as 80%. Enzymatic studies indicated that CSC is a potent inhibitor of cytochrome P-450 dependent monooxygenase. Therefore, it appears that CSC exerts its antimutagenic effect by way of inhibition of the P-450 system.

Lee *et al.* (1994) also reported that fractionation of the CSC yielded fractions which showed low mutagenicity but significant antimutagenicity.

## APPENDIX A. COMPONENTS IDENTIFIED IN SIDESTREAM SMOKE

Identified MS components number about 4,800; identified SS components number over 300. As noted in the text, there is no logical reason to believe that SS composition differs qualitatively from that of MS. However, the compositions will differ quantitatively from each other and from ETS.

With sufficient time and effort, the compounds already identified in MS could eventually be identified in SS. **Table 35** summarizes the compound classes into which the 320 identified SS components fall and the number of identified components in each class. Of these 320, nearly 180 have been identified by R. J. Reynolds Tobacco Company (RJRT) R & D personnel; 109 of these have been identified by RJRT personnel only.

**Table 36** lists the 319 individual components identified to date in SS.

**TABLE 35: IDENTIFIED SS COMPONENTS: BY COMPOUND CLASS**

| | Number Reported | | |
|---|---|---|---|
| Component Class | Total | By RJRT Only | By RJRT Only or RJRT *et al.* |
| Hydrocarbons: Aliphatic | 11 | 1 | 3 |
| Monocyclic | 11 | 5 | 7 |
| Polycyclic | 19 | 1 | 6 |
| Acids | 15 | 1 | 4 |
| Alcohols and phenols | 36 | 12 | 19 |
| Aldehydes | 14 | 9 | 14 |
| Ketones | 29 | 21 | 26 |
| Esters and lactones | 8 | 6 | 6 |
| Amides | 6 | 3 | 5 |
| Amines | 131 | 46 | 70 |
| *N*-Nitrosamines | 9 | 0 | 6 |
| Nitriles | 7 | 2 | 3 |
| Miscellaneous components | 23 | 2 | 9 |
| Total | 319 | 109 | 178 |

## TABLE 36: IDENTIFIED SS COMPONENTS

| Component | R. J. Reynolds Tob. Co. (1988) | Klus & Kuhn (1982) | Eatough *et al.*, (1990b)[b] | Sakuma *et al.*, (1983a, 1983b; 1984a, 1984b) | Brunne-mann *et al.*, (1990) | IARC (1986) |
|---|---|---|---|---|---|---|
| | | HYDROCARBONS | | | | |
| *Aliphatic Hydrocarbons* | | | | | | |
| acetylene | | X | | | | |
| 1,3-butadiene | | | X | | | |
| ethene | | | X | | | |
| *n*-hentriacontane | | | X | | | |
| isoprene | | | X | | | |
| limonene | X | | X | | X | |
| methane | | X | | | | |
| neophytadiene | X | | X | | | |
| pentadecane | X | | | | | |
| propane | | X | | | | |
| propene | | | X | | | |
| *Monocyclic Hydrocarbons* | | | | | | |
| **benzene**[a] | X | X | | | X | X[c] |
| benzene, 1,2-dimethyl- [o-*xylene*] | | X | | | | |
| benzene, 1,3-dimethyl- [m-*xylene*] | | X | | | | |
| benzene, 1,4-dimethyl- [p-*xylene*] | | X | | | | |
| **benzene, ethenyl- [styrene]**[a] | X | X | | | | |
| benzene, ethyl- | X | | | | | |
| benzene, isopropyl- | X | | | | | |
| benzene, methyl- [toluene] | | X | | | X | X[c] |
| benzene, (1-methylethyl)- [*cumene*] | X | | | | | |
| benzene, trimethyl- | X | | | | | |
| *p*-cymene | X | | | | | |
| *Polycyclic Hydrocarbons* | | | | | | |
| anthracene | | | X | | | |
| **benz[*a*]anthracene**[a] | X | X | | | | |
| benzo[*ghi*]perylene | | | X | | | X[c] |
| **benzo[*a*]pyrene**[a] | X | | X | | | X[c] |
| benzo[*e*]pyrene | | | X | | | X[c] |
| cholesta-3,5-diene, 24-ethyl- | | X | X | | | |
| cholesta-3,5,22-triene, 24-methyl- | | | X | | | |
| coronene | | | | | | X[c] |
| dibenz[*a,j*]anthracene | | | | | | X[c] |
| dibenzo[*def,mno*]chrysene [*anthanthrene*] | | | | | | X[c] |
| fluoranthene | | | X | | | X |
| **indeno[1,2,3-*cd*]pyrene**[a] | | | X | | | |
| naphthalene | X | X | X | | | |
| naphthalene, 1,6-dimethyl- | X | | | | | |
| naphthalene, 1-methyl- | X | X | | | | |



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**Table 36: Continued**

| Component | R. J. Reynolds Tob. Co. (1988) | Klus & Kuhn (1982) | Eatough et al., (1990b)[b] | Sakuma et al., (1983a, 1983b; 1984a, 1984b) | Brunnemann et al., (1990) | IARC (1986) |
|---|---|---|---|---|---|---|
| | | HYDROCARBONS (cont.) | | | | |
| *Polycyclic Hydrocarbons (cont.)* | | | | | | |
| naphthalene, 2-methyl- | X | X | | | | |
| perylene | | | | | | c |
| phenanthrene | | X | X | | | X |
| pyrene | | X | X | | | X[c] |
| | | ACIDS | | | | |
| acetic acid | X | | X | X | | X |
| benzoic acid | | | X | X | | X |
| benzoic acid, 2-hydroxy- | | | X | X | | |
| formic acid | X | | X | X | | X |
| 2-furoic acid | | | X | X | | |
| glutaric acid | | | X | X | | |
| glycolic acid | | | X | X | | X |
| lactic acid | | | X | X | | X |
| levulinic acid | | | X | X | | |
| pentanoic acid, 3-methyl- | X | | X | X | | |
| phenylacetic acid | | | X | X | | |
| propanoic acid | X | | | | | |
| propanoic acid, 3-hydroxy- | | | X | X | | |
| succinic acid | | | X | X | | X |
| succinic acid, methyl- | | | X | X | | |
| | | ALCOHOLS AND PHENOLS | | | | |
| allyl alcohol | X | | | | | |
| 1,2-benzenediol [*catechol*] | | | X | X | | X |
| 1,2-benzenediol, 4-ethyl- | | | X | X | | |
| 1,2-benzenediol, 3-methyl- | | | X | X | | |
| 1,2-benzenediol, 4-methyl- | | | X | X | | |
| 1,2-benzenediol, 3-ethenyl- | | | X | X | | |
| 1,4-benzenediol [*hydroquinone*] | X | | X | X | | |
| 1,4-benzenediol, methyl- | | | X | X | | |
| benzyl alcohol | X | | | | | |
| campesterol | | | X | | | X |
| cholesterol | | X | X | | | X |
| 2-cyclopentenone, 2-hydroxy-3-methyl- | | | X | | | |
| 1-decanol | X | | | | | |
| 1,2-ethanediol | X | | | | | |
| 2-furanmethanol | X | | X | | | |
| glycerol | X | | | | | X |
| guaiacol | | X | X | X | | X |
| guaiacol, 4-ethenyl- | | | X | X | | |



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Table 36: Continued

| Component | R. J. Reynolds Tob. Co. (1988) | Klus & Kuhn (1982) | Eatough *et al.*, (1990b)[b] | Sakuma *et al.*, (1983a, 1983b; 1984a, 1984b) | Brunnemann *et al.*, (1990) | IARC (1986) |
|---|---|---|---|---|---|---|
| | ALCOHOLS AND PHENOLS (*cont.*) | | | | | |
| 1-heptanol | X | | | | | |
| phenethanol | X | | | | | |
| phenol | X | X | X | X | | X |
| phenol, 2,6-dimethoxy-4-ethenyl- | X | | | | | |
| phenol, dimethyl- [*xylenol*] | | X | | | | |
| phenol, 2,6-dimethyl- [*2,6-xylenol*] | X | | X | X | | |
| phenol, 3,4-dimethyl- [*3,4-xylenol*] | X | | | | | |
| phenol, ethyl- | | X | | | | |
| phenol, 2-ethyl- | X | | | | | |
| phenol, 2-methyl- [o-*cresol*] | | | X | X | | |
| phenol, 3-methyl- [m-*cresol*] | X | | X | X | | |
| phenol, 4-methyl- [p-*cresol*] | X | | X | X | | |
| phenol, 4-ethenyl- | | | X | X | | |
| 1,2-propanediol | X | | | | | X |
| 1,2-propanediol, 3-chloro- | X | | | | | |
| β-sitosterol | | | X | X | | X |
| solanesol | X | | X | | | X |
| stigmasterol | | X | X | | | X |
| | ALDEHYDES | | | | | |
| acetaldehyde[a] | X | | | | | |
| acrolein | X | X | X | | | X[c] |
| benzaldehyde | X | | | | | |
| crotonaldehyde[a] | X | | | | | |
| formaldehyde[a] | X | X | X | | | X |
| 2-furaldehyde | X | | X | | | |
| 2-furaldehyde, 5-methyl- | X | | X | | | |
| 3-furaldehyde | X | | | | | |
| *cis*-3-hexenal | X | | | | | |
| methacrolein | X | | | | | |
| 2-nonenal | X | | | | | |
| propionaldehyde | X | X | | | | |
| propionaldehyde, 2,2-dimethyl- | X | | | | | |
| propionaldehyde, 3-methylthio- | X | | | | | |
| | KETONES | | | | | |
| acetol | X | | | | | |
| acetone | X | X | X | | | X |
| acetophenone, 4-methyl- | X | | | | | |
| 2,3-butanedione | | X | | | | |
| butanone | | X | | | | |
| 1-buten-3-one [*methyl ethenyl ketone*] | | X | | | | |

## Table 36: Continued

| Component | R. J. Reynolds Tob. Co. (1988) | Klus & Kuhn (1982) | Eatough et al., (1990b)[b] | Sakuma et al., (1983a, 1983b; 1984a, 1984b) | Brunnemann et al., (1990) | IARC (1986) |
|---|---|---|---|---|---|---|
| | KETONES (cont.) | | | | | |
| 2-cyclopentanone | X | | | | | |
| 2-cyclopentanone, 2 (or 3)-methyl- | X | | | | | |
| 2-cyclopentenone | X | | X | | | |
| 2-cyclopentenone, dimethyl- | X | | | | | |
| 2-cyclopentenone, 2,3-dimethyl- | X | | X | | | |
| 2-cyclopentenone, 2,4-dimethyl- | X | | | | | |
| 2-cyclopentenone, 2-hydroxy-3-methyl- | X | | | | | |
| 2-cyclopentenone, 2-methyl- | X | | X | | | |
| 2-cyclopentenone, 3-methyl- | X | | | | | |
| 1,3-dioxolan-2-one, 4-hydroxymethyl- | X | | | | | |
| 9-fluorenone | X | | | | | |
| 2(3*H*)-furanone, 4,5-dihydro- | X | | | | | |
| 2(3*H*)-furanone, 4,5-dihydro-4-hydroxy- | X | | | | | |
| 2(3*H*)-furanone, 4,5-dihydro-5-hydroxymethyl- | X | | | | | |
| 2(3*H*)-furanone, 4,5-dihydro-4-methyl- | X | | | | | |
| 2(5*H*)-furanone | X | | | | | |
| 2(5*H*)-furanone, 3-methyl- | X | | | | | |
| 2(5*H*)-furanone, 4-methyl- | X | | | | | |
| 2(5*H*)-furanone, 5-methylene- [*protoanemonin*] | X | | | | | |
| 1-indanone | X | | | | | |
| 2-indanone | X | | | | | |
| 4-keto-β-ionol, dihydro- | X | | | | | |
| 2-pentanone | X | X | | | | |
| | ESTERS AND LACTONES | | | | | |
| acetic acid, 2-hydroxyethyl ester | X | | | | | |
| acetic acid, hydroxyphenol ester | X | | | | | |
| butyrolactone | | | X | | | X |
| furan, 2-acetyl- | X | | | | | |
| phthalic acid, dibutyl ester | X | | | | | |
| phytosteryl esters | | | | | | X |
| 1,2,3-propanetriol, acetate [*monoacetin*] | X | | | | | |
| 1,2,3-propanetriol, triacetate [*triacetin*] | X | | | | | |
| | AMIDES | | | | | |
| acetamide | X | | X | | | X |
| acetamide, *N*-methyl- | X | | | | | |
| acrylamide, 2-methyl- | X | | | | | |
| butyramide | X | | | | | |
| formamide | | | | | | X |
| propionamide | X | | | | | X |



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**Table 36: Continued**

| Component | R. J. Reynolds Tob. Co. (1988) | Klus & Kuhn (1982) | Eatough *et al.*, (1990b)[b] | Sakuma *et al.*, (1983a, 1983b; 1984a, 1984b) | Brunnemann *et al.*, (1990) | IARC (1986) |
|---|---|---|---|---|---|---|
| | | AMINES | | | | |
| *n*-amylamine | | | X | | | |
| acridine | | X | | | | |
| anabasine, *N*-methyl- | | | | X | | |
| anatabine | | | | X | | X |
| aniline | | X | X | | | X |
| aniline, 2,3-dimethyl- [*2,3-xylidine*] | | X | | | | X |
| aniline, 2,4-dimethyl- [*2,4-xylidine*] | | X | | | | X |
| aniline, 2,5-dimethyl- [*2,5-xylidine*] | | X | | | | X |
| aniline, 2,6-dimethyl- [*2,6-xylidine*] | | X | | | | X |
| aniline, 2-ethyl- | | X | | | | X |
| aniline, 3-ethyl- | | X | | | | X |
| aniline, 4-ethyl- | | X | | | | X |
| **aniline, 2-methyl- [*2-toluidine*][a]** | | X | | | | X |
| aniline, 3-methyl- [*3-toluidine*] | | X | | | | X |
| aniline, 4-methyl- [*4-toluidine*] | | X | | | | X |
| benzimidazole | | | | X | | |
| benzimidazole, 1-methyl- | | | | X | | |
| benzo[*h*]quinoline | | X | | | | |
| biphenyl, 2-amino- | | X | | | | X |
| biphenyl, 3-amino- | | X | | | | X |
| **biphenyl, 4-amino-[a]** | | | X | | | |
| 2,3'-bipyridine | X | | | X | | |
| 2,3'-bipyridine, methyl- | X | | | | | |
| 2,3'-bipyridine, 5-methyl- | | | | X | | |
| 2,4'-bipyridine | X | | | | | |
| 3,3'-bipyridine | X | | | | | |
| butylamine | | | | X | | |
| cotinine | X | | X | X | | |
| dimethylamine | | | X | X | | X |
| dipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-5,10-diol [*pyrocoll*] | X | | | | | |
| ethylamine | | | | X | | |
| harman | | X | | | | X |
| hydantoin, 1-methyl- | X | | | | | |
| imidazole | X | | | | | |
| imidazole, 2-butyl- | X | | | | | |
| imidazole, 1,4-dimethyl- | X | | | | | |
| imidazole, 2,4-dimethyl- | X | | | | | |
| imidazole, 4,5-dimethyl- | X | | | | | |
| imidazole, 4-ethyl- | X | | | | | |
| imidazole, 1-methyl | X | | | | | |
| imidazole, 2-methyl- | X | | | X | | |

Table 36: Continued

| Component | R. J. Reynolds Tob. Co. (1988) | Klus & Kuhn (1982) | Eatough *et al.*, (1990b)[b] | Sakuma *et al.*, (1983a, 1983b; 1984a, 1984b) | Brunne-mann *et al.*, (1990) | IARC (1986) |
|---|---|---|---|---|---|---|
| | AMINES *(cont.)* | | | | | |
| imidazole, 4-methyl- | X | | | X | | |
| imidazole, 1,2,4-trimethyl- | X | | | | | |
| imidazole, 2,4,5-trimethyl- | X | | | | | |
| 1*H*-indole | X | | X | | | |
| 1*H*-indole, dimethyl- | X | | | | | |
| 1*H*-indole, 2-methyl- | X | | | | | |
| 1*H*-indole, 3-methyl- [*skatole*] | X | | | | | |
| 1*H*-indole, 4(or 5)-methyl- | X | | | | | |
| isoamylamine | | | X | X | | |
| isobutylamine | | | | X | | |
| isopropylamine | | | X | | | |
| isoquinoline | X | | X | X | | |
| methylamine | | | X | X | | X |
| myosmine | X | | X | X | | |
| 1-naphthylamine | | X | | | | X |
| 1-naphthylamine, 2-methyl- | | X | | | | X |
| **2-naphthylamine**[a] | | | X | | | X |
| 1,8-naphthyridine | X | | | | | |
| nicotinamide, *N*-methyl- | X | | | | | |
| nicotine | X | X | X | X | | X[c] |
| nicotyrine | X | | X | X | | |
| norharman | | X | | | | |
| nornicotine, *N*-formyl- | X | | | | | |
| propylamine | | | | X | | |
| pyrazine | X | | | | | |
| pyrazine, 2,3-dimethyl- | | X | | | | X |
| pyrazine, 2,5-dimethyl- | X | | | X | | |
| pyrazine, 2,6-dimethyl- | X | | | | | |
| pyrazine, ethyl- | X | | | | | |
| pyrazine, 2-ethyl-6-methyl- | X | | | | | |
| pyrazine, 2-(2-furyl)-5-methyl- | X | | | | | |
| pyrazine, hydroxymethyl- | X | | | | | |
| pyrazine, methyl- | X | | | X | | X |
| pyrazine, trimethyl- | X | | | | | |
| pyrazine, ethenyl- | X | | | | | |
| pyridine | X | X | X | X | X | X |
| pyridine, 2-acetyl- | | | X | X | | |
| pyridine, 3-acetyl- | | | | X | | |
| pyridine, 2-amino- | X | | | | | |
| pyridine, 3-amino- | X | | | | | |
| pyridine, 4-*tert*-butyl- | | X | | X | | |
| pyridine, 3-cyano- | X | | X | X | | |



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## Table 36: Continued

| Component | R. J. Reynolds Tob. Co. (1988) | Klus & Kuhn (1982) | Eatough *et al.*, (1990b)[b] | Sakuma *et al.*, (1983a, 1983b; 1984a, 1984b) | Brunne-mann *et al.*, (1990) | IARC (1986) |
|---|---|---|---|---|---|---|
| | AMINES *(cont.)* | | | | | |
| pyridine, 4-cyano- | X | | | | | |
| pyridine, dimethyl- [*lutidine*] | X | | | | | |
| pyridine, 2,3-dimethyl- [*2,3-lutidine*] | | X | | X | | |
| pyridine, 2,4-dimethyl- [*2,4-lutidine*] | | | X | X | | X |
| pyridine, 2,5-dimethyl- [*2,5-lutidine*] | | X | | X | | X |
| pyridine, 2,6-dimethyl- [*2,6-lutidine*] | X | X | | X | | X |
| pyridine, 3,4-dimethyl- [*3,4-lutidine*] | | X | | | | |
| pyridine, 3,5-dimethyl- [*3,5-lutidine*] | | X | | X | | |
| pyridine, 3-ethyl- | X | X | X | X | | |
| pyridine, 3-ethyl-4-methyl- | | X | | | | |
| pyridine, 4-ethyl- | | X | | | | |
| pyridine, 3-hydroxy- | | | X | X | | |
| pyridine, 3-hydroxy-4-methyl- | X | | | | | |
| pyridine, 2-methyl- [*2-picoline*] | X | X | | X | X | X |
| pyridine, 3-methyl- [*3-picoline*] | X | X | | X | X | X |
| pyridine, 4-methyl- [*4-picoline*] | X | X | | X | X | X |
| pyridine, methylethenyl- | | | | X | | |
| pyridine, 2-(3-pentyl)- | | | X | | | |
| pyridine, 3-phenyl- | | | | X | | |
| pyridine, 2,4,6-trimethyl- [*collidine*] | X | X | | X | | |
| pyridine, 2-ethenyl- | X | | X | | | |
| pyridine, 3-ethenyl- | X | X | X | X | X | X |
| 3-pyridinol | X | | | | | |
| 3-pyridinol, 6-ethyl- | X | | | | | |
| 2(1*H*)-pyridone, 5,6-dihydro- | X | | | X | | |
| pyrrole | X | | X | X | | |
| pyrrole, 3-acetyl- | X | | | | | |
| pyrrole, 2-methyl- | X | | | | | |
| pyrrole, 3-methyl- | X | | | | | |
| pyrrole-2-carboxaldehyde | X | | | | | |
| pyrrolidine | | | X | X | | |
| pyrrolidine, *N*-methyl- | | | X | X | | |
| 2,5-pyrrolidinedione, 3-ethyl-1-methyl- | X | | | | | |
| 2-pyrrolidinone | X | | | | | |
| 3-pyrrolidin-2-one, 3-methyl- | X | | | X | | |
| pyrrolidinone, *N*-methyl- | X | | | | | |
| 1*H*-pyrrolo[2,3-*b*]pyridine, *N*-methyl- | X | | | | | |
| 1*H*-pyrrolo[2,3-*b*]pyridine, methyl- | X | | | | | |
| **quinoline**[a] | | X | X | X | | X |
| quinoline, 3,6-dimethyl- | | X | | | | |
| quinoline, ethyl- | | X | | | | |
| quinoline, methyl- | | X | | | | |



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Table 36: Continued

| Component | R. J. Reynolds Tob. Co. (1988) | Klus & Kuhn (1982) | Eatough *et al.*, (1990b)[b] | Sakuma *et al.*, (1983a, 1983b; 1984a, 1984b) | Brunne-mann *et al.*, (1990) | IARC (1986) |
|---|---|---|---|---|---|---|
| AMINES *(cont.)* | | | | | | |
| quinoline, 4-methyl- | | X | | | | |
| quinoline, 5-methyl- | | X | | | | |
| quinoline, 7-methyl- | | X | | | | |
| quinoline, 8-methyl- | | X | | | | |
| quinoline, propyl- | | X | | | | |
| 1,3,5,7-tetraazatricyclo-(3,3,1,1,3,7)-decane [*hexamethylenetetramine*] | X | | | | | |
| *N*-NITROSAMINES | | | | | | |
| 1-butanone, 4-(methylnitrosamino)-1-(3-pyridinyl)- [*NNK*][a] | X | X | X | | | X |
| **N'-nitrosoanabasine [*NAB*][a]** | X | | | | | |
| *N'*-nitrosoanatabine [*NAT*] | X | X | | | | |
| **N-nitrosodiethanolamine [*NDELA*][a]** | | | | | | X |
| **N-nitrosodiethylamine [*NDEA*][a]** | | X | | | | |
| **N-nitrosodimethylamine [*NDMA*][a]** | X | X | X | | | X |
| **N-nitrosoethylmethylamine [*NEMA*][a]** | | X | | | | X |
| **N'-nitrosonornicotine [*NNN*][a]** | X | X | X | | | X |
| **N-nitrosopyrrolidine [*NPYR*][a]** | X | X | X | | | X |
| NITRILES | | | | | | |
| acetonitrile | X | X | X | | | |
| acetonitrile, 2-(*N,N*-dimethylamino)- | X | | | | | |
| benzonitrile | X | | | | | |
| butyronitrile | | X | | | | |
| isovaleronitrile | | X | | | | |
| propionitrile | | X | | | | |
| valeronitrile | | X | | | | |
| MISCELLANEOUS COMPONENTS | | | | | | |
| ammonia | X | X | X | | | X |
| benzofuran, 2,3-dihydro- | X | | | | | |
| benzofuran, 2-methyl- | X | | | | | |
| bromide | | X | | | | |
| **cadmium[a]** | | X | | | | |
| carbon dioxide | X | X | X | | | |
| carbon monoxide | X | X | X | | | X[c] |
| carbonyl sulfide | | X | | | | X |
| chloride | | X | | | | |
| furan, methyl- | | X | | | | |
| **hydrazine[a]** | | | | | | X |
| hydrogen cyanide | X | X | X | | | X |



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## Table 36: Continued

| Component | R. J. Reynolds Tob. Co. (1988) | Klus & Kuhn (1982) | Eatough *et al.*, (1990b)[b] | Sakuma *et al.*, (1983a, 1983b; 1984a, 1984b) | Brunne-mann *et al.*, (1990) | IARC (1986) |
|---|---|---|---|---|---|---|
| | | | MISCELLANEOUS COMPONENTS *(cont.)* | | | |
| **lead**[a] | | X | | | | |
| methyl bromide | | | | | | X |
| methyl chloride | | X | | | | X |
| **nickel**[a] | | X | | | | X |
| nitric acid | | | X | | | |
| nitric oxide | X | | | X | | X |
| nitrogen dioxide | X | | X | | | X |
| "nitrogen oxides" [NOx] | X | | X | | | X[c] |
| nitrous acid | | | X | | | |
| **polonium-210**[a] | | | | | | X |
| zinc | | X | | | | X |

[a] Components in bold lettering appear in one or other of the two "Lists of 43" (Hoffmann and Hecht, 1990; OSHA, 1994) (see Table 4).
[b] Components listed by Eatough *et al.* (1990b) are identified ETS components not SS components.
[c] This component was discussed as an ETS component in the Surgeon General's 1986 report (USPHS, 1987).



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# BIBLIOGRAPHY


ACGIH (1990), *Documentation of the Threshold Limit Values and Biological Exposure Indices*. 5th Ed. plus Supplements (1986-1990), ACGIH, Cincinnati OH.

Adams JD, Lee SJ, Vinchkoski N, Castonguay A, and Hoffmann D (1983), On the Formation of the Tobacco-Specific Carcinogen 4-(Methylnitrosamino)-1-(3-pyridyl)butanone during Smoking. CANCER LETT. *17:* 336-346.

Adams JD, O'Mara-Adams KJ, and Hoffmann D (1987), Toxic and Carcinogenic Agents in Undiluted Mainstream Smoke and Sidestream Smoke of Different Types of Cigarettes. CARCINOGENESIS *8:* 729-731.

Adlkofer FX, Scherer G, von Meyerinck L, von Maltzan C, and Jarczyk L (1989), Exposure to ETS and Its Biological Effects: A Review. In Bieva CJ, Courtois Y, and Govaerts M (Editors), *Present and Future of Indoor Air Quality*, Elsevier Science Publishers BV (Biomedical Division), Amsterdam: 183-196.

Adlkofer FX, Scherer G, and Westphal K (1988), Estimation of Exposure to Tobacco Smoke by Active and Passive Smoking. EUROPEAN MTG. TOXICOL. FORUM, Lyon, France.

Ahlmann J (1958), Detection of Polycyclic Aromatic Hydrocarbons in Cigarette Tar. ACTA PATHOL. MICROBIOL. SCAND. *43:* 379-390.

Alldrick AJ, Cottrell RC, Rowland IR, and Gangolli SD (1985), The Role of DNA-Repair Processes in *N*-Nitrosopyrrolidine-Induced Mutagenesis. CARCINOGENESIS *6:* 105-108.

American Association for Cancer Research (1984). *Position Paper on Carcinogens in Tobacco [Smoke].*

American Meat Institute (1980), FOOD TECHNOL. *34:* 45-51.

Andervont HB and Shimkin MB (1940), J. NATL. CANCER INST. *1:* 225-239.

Archer MC, Tannenbaum SR, Fan TY, and Weisman M (1975), Reaction of Nitrite with Ascorbate and Its Relation to Nitrosamine Formation. J. NATL. CANCER INST. *54:* 1203-1205.

Arundel A, Sterling T, and Weinkam J (1988), Exposure and Risk-Based Estimates of Never Smoke Lung Cancer Deaths in U.S. in 1980 from Exposure to ETS. In Perry R and Kirk PW (Editors), *Indoor and Ambient Air Quality*, Selper Ltd., London UK: 424-251.

Auerbach O, Hammond EC, Kirman D, and Garfinkel L (1970), II. Pulmonary Neoplasms. ARCH ENVIRON. HLTH. *21:* 754-768.

Aviado DM (1988), Suspected Pulmonary Carcinogens in Environmental Tobacco Smoke. ENVIRON. TECH. LETT. *9:* 539-544.

Aviado DM (1990), Non-Epidemiological Studies on Potential Carcinogens in Environmental Tobacco Smoke: A Critique of the Environmental Protection Agency's Designation of Environmental Tobacco Smoke as a Group A Carcinogen. Documented submitted to the Environmental Protection Agency (September 25).

Aviado DM (1993), Complex Mixtures of Tobacco Smoke and the Occupational Environment. Chapter 4 in Clayton GD and Clayton FE (Editors), *Patty's Industrial Hygiene and Toxicology, 4th Edition, Vol. 2, Pt. A*, John Wiley and Sons, Inc. New York NY: 107-148.

Badger GM, Donnelly JK, and Spotswood TM (1965), The Formation of Aromatic Hydrocarbons at High Temperatures. XXIV. The Pyrolysis of Some Tobacco Constituents. AUSTRALIAN J. CHEM. *18:* 1249-1266.

Badger GM, Donnelly JK, and Spotswood TM (1966), The Formation of Aromatic Hydrocarbons at High Temperatures. XXVII. The Pyrolysis of Isoprene. AUSTRALIAN J. CHEM. *19:* 1023-1043.

Bailey D, Doerr R, Fiddler W, and Fairheller S (1982), Unhairing Method Identified as Source of *N*-Nitrosodimethylamine in Tannery Atmosphere. J. AM. LEATHER. CHEM. ASSOC. *77:* 476-484.

Bailey GS and Williams DE (1993), Potential Mechanisms for Food-Related Carcinogens and Anticarcinogens: A Scientific Status Summary by the Institute of Food Technologists' Expert Panel on Food Safety & Nutrition. FOOD TECHNOL. 105-118.

Baker RR (1976), The Kinetics of Tobacco Pyrolysis. THERMOCHIM. ACTA *17:* 29-63.

Baker RR (1979), Kinetic Mechanisms of the Thermal-Decomposition of Tobacco. THERMOCHIM. ACTA *28,N1:* 45-57.

Baker RR (1980), Mechanisms of Smoke Formation and Delivery. RECENT ADV. TOB. SCI. *6:* 184-224.

Baker RR (1984), The Effect of Ventilation on Cigarette Combustion Mechanisms. RECENT ADV. TOB. SCI. *10:* 88-150.

Baker RR (1987a), A Review of Pyrolysis Studies to Unravel Reaction Steps in Burning Tobacco. J. ANAL. APPL. PYROL. *11:* 555-573.

Baker RR (1987b), Some Burning Problems in Tobacco Science. PROCEEDINGS OF THE INTERNATIONAL CONFERENCE ON PHYSICAL AND CHEMICAL PROCESSES OCCURRING IN A BURNING CIGARETTE. R. J. Reynolds Tobacco Company, Winston-Salem NC: 1-61.

Baker RR and Robinson DP (1990), Tobacco Combustion - The Last Ten Years. RECENT ADV. TOB. SCI. *16:* 3-71.

Barnes JM (1974), Nitrosamines. In WJ Hayes Jr (Editor), *Essays in Toxicology Vol. 5,* Academic Press, New York NY: 5-15.

Barnes JM and Magee PN (1954), Some Toxic Problems of Dimethylnitrosamine. BRIT. J. IND. MED. *11:* 167-174.

Barry G, Cook JW, Haslewood GAD, Hewett CL, Hieger I, and Kennaway EL (1935), The Production of Cancer by Pure Hydrocarbons. Part III. PROC. ROY. SOC. (BIOL.) *117:* 318-351.

Bassir O and Maduagwu EN (1978), J. AGR. FOOD CHEM. *26:* 200-203.

Bayer CW and Black MS (1987), Thermal Desorption/Gas Chromatographic/Mass Spectrometric Analysis of Volatile Organic Compounds in the Offices of Smokers and Nonsmokers. BIOMED. ENVIRON. MASS SPECTROMETRY *14:* 363-367.

Bell JH, Saunders AO, and Spears AW (1966), The Contribution of Tobacco Constituents to Phenol Yield of Cigarettes. TOB. SCI. *10:* 138-142.

Benner CF, Burton HR, and Burdick D (1969a), Correlation Between the Amounts of Various Leaf Constituents and the Levels of Nicotine, Phenols, and Benzo[*a*]pyrene in the Smoke Condensate. 23rd TOB. CHEM. RES. CONF., Philadelphia PA: Paper No. 18.

Benner CF, Burton HR, and Burdick D (1969b), Temperature-Yield Profiles of Tobacco and Tobacco Constituents. I. Borate-Treated and Untreated Tobacco. BEITR. TABAKFORSCH. *5:* 74-79.

Benner CL, Bayona JM, Caka FM, Tang H, Lewis L, Crawford J, Lamb J, Lee ML, Lewis EA, Hansen LD, and Eatough DJ (1989), Chemical Composition of Environmental Tobacco Smoke. 2. Particulate Phase Compounds. ENVIRON. SCI. TECHNOL. *23:* 688-699.

Berenblum I and Schoental R (1947), The Carcinogenic Constitution of Coal Tar. BRIT. J. CANCER *1:* 157-165; CANCER RES. *7:* 390-392.

Bernfeld P, Homburger F, and Russfield AB (1974), Strain Differences in the Response of Inbred Syrian Hamsters to Cigarette Smoke Inhalation. J. NATL. CANCER INST. *53:* 1141-1157.

Bombick DW, Ayres PH, Nelson P, Coggins CRE, France D, Fulp C, Lee CK, and Doolittle DJ (1991), Assessment of the Biological Activity of Mainstream or Environmental Tobacco Smoke (ETS) Using a Cellular Smoke Exposure Technique. NATL. ENVIRON. MUTAGEN SOC. MTG., Orlando FL.

Bonnet J (1958), What Carcinogenic Substances Have Been Demonstrated to be Present in Tobacco Smoke Condensate. PROC. 1st WORKSHOP CONF. ON LUNG CANCER RES. (APP. A): 27-30.

Bonnet J (1962), Quantitative Analysis of Benzo(a)pyrene in Vapors Coming from Melted Tar. *Symp. on Analysis of Carcinogenic Air Pollutants,* NATL. CANCER INST. MONOGRAPH *9:* 221-223.

Bonnet J and Neukomm S (1956), Sur la Composition Chimique de la Fumée du Tabac. I. Analyse de la Fraction Neutre. HELV. CHIM. ACTA *39:* 1724-1733.

Bonnet J and Neukomm S (1957), Résultats Actuels des Recherches Chimiques sur la Composition de la Fumée du Tabac. ONCOLOGIA *10:* 124-129.

Bonnet J and Neukomm S (1959a), Carcinogenic and Cocarcinogenic Substances in Tobacco Smoke. ACTA UNIO INTERNAT. CONTRA CANC. *15:* 561-563.

Bonnet J and Neukomm S (1959b), New Investigations on Carcinogenic Substances in Tobacco. ONCOLOGIA *12:* 80-86.

Bos BP, Theuws JLG, and Henderson PT (1983), Excretion of Mutagens in Human Urine after Passive Smoking. CANCER LETT. *19:* 85-90.

Boyland E, Gorrod JW, Roe FJC, and Mitchley BVC (1964a), The Carcinogenicity of Nitrosoanabasine, A Possible Constituent of Tobacco Smoke. BRIT. EMP. CANCER CAMP., ANN. RPT. *41:* 64.

Boyland E, Nice E, and Williams K (1971), The Catalysis of Nitrosation by Thiocyanate from Saliva. FOOD COSMET. TOXICOL. *9:* 639-643.

Boyland E, Roe FJC, and Gorrod JW (1964b), Induction of Pulmonary Tumours in Mice by Nitrosonornicotine, A Possible Constituent of Tobacco Smoke. NATURE *202:* 1126.

Boyland E, Roe FJC, Gorrod JW, and Mitchley BVC (1964c), The Carcinogenicity of Nitrosoanabasine, A Possible Constituent of Tobacco Smoke. BRIT. J. CANCER *18:* 265-272.

Brunnemann KD, Adams JD, Ho DPS, and Hoffmann D (1978), The Influence of Tobacco Smoke on Indoor Atmospheres. II. Volatile and Tobacco-Specific Nitrosamines in Mainstream and Sidestream Smoke and Their Contribution to Indoor Pollution. PROC. 4th JOINT CONF. ON SENSING OF ENVIRONMENTAL POLLUTANTS, 1977, New Orleans LA, AM. CHEM. SOC: 876-880.

Brunnemann KD, Cox JE, and Hoffmann D (1992), Analysis of Tobacco-Specific *N*-Nitrosamines in Indoor Air. CARCINOGENESIS *13:* 2415-2418.

Brunnemann KD, Cox JE, Kagan R, and Hoffmann D (1990a), Application of Thermal Desorption for the Analysis of Environmental Tobacco Smoke (ETS). 44th TOB. CHEM. RES. CONF., Winston-Salem NC: Paper No. 27.

Brunnemann KD, Cox JE, Kagan R, and Hoffmann D (1990b), Analysis of Selected Environmental Tobacco Smoke Components in Indoor Air by Thermal Desorption-GC-MS. CORESTA 1990 SYMP., Halithea, Greece, CORESTA INF. BULL., Spec. Edition, 1990: Paper S10, 216.

Brunnemann KD and Hoffmann D (1981). Assessment of the Carcinogenic *N*-Nitrosodiethanolamine in Tobacco Products and Tobacco Smoke. CARCINOGENESIS *2:* 1123-1127.

Brunnemann KD and Hoffmann D (1982), Pyrolytic Origins of Major Gas Phase Constituents of Cigarette Smoke. RECENT ADV. TOB. SCI. *8:* 103-140.

Brunnemann KD and Hoffmann D (1983a), *N*-Nitrosodiethanolamine in Tobacco and Mainstream and Sidestream Smoke. In Egan H, Preussmann R, Eisenbrand G, Spiegelhalder T, O'Neill IK, and Bartsch H (Editors), *Environmental Carcinogens. Selected Methods of Analysis. Vol. 6: N-Nitroso Compounds*. IARC, Lyon, France, IARC SCI. PUBL. NO. 45: 85-92.

Brunnemann KD and Hoffmann D (1983b), GC-TEA of *N*-Nitrosodiethanolamine (NDELA) from Tobacco Products. In Egan H, Preussmann R, Eisenbrand G, Spiegelhalder T, O'Neill IK, and Bartsch H (Editors), *Environmental Carcinogens. Selected Methods of Analysis. Vol. 6: N-Nitroso Compounds*. IARC, Lyon, France, IARC SCI. PUBL. NO. 45: 399-402.

Brunnemann KD and Hoffmann D (1991a), Analytical Studies on *N*-Nitrosamines in Tobacco and Tobacco Smoke. RECENT ADV. TOB. SCI. *17:* 71-112.

Brunnemann KD and Hoffmann D (1991b), Analytical Studies on Tobacco-Specific *N*-Nitrosamines in Tobacco and Tobacco Smoke. CRIT. REV. TOXICOL. *21:* 235-240.

Brunnemann KD, Scott JC, Haley NJ, and Hoffmann D (1984b), Endogenous Formation of *N*-Nitrosoproline upon Cigarette Smoke Inhalation. In O'Neill IK, von Borstel RC, Miller CT, Long J, and Bartsch H (Editors), *N-Nitroso Compounds: Occurrence, Biological Effects and Relationship to Human Cancer*, IARC, Lyon, France, IARC SCI. PUBL. NO. 57: 819-828.

Brunnemann KD, Yu L, and Hoffmann D (1977), Assessment of Carcinogenic Volatile *N*-Nitrosamines in Tobacco and Mainstream and Sidestream Smoke from Cigarettes CANCER RES. *37:* 3218-3222.

Caldwell WS and Conner JM (1989), Artifact Formation during Smoke Trapping. An Improved Method for the Determination of *N*-Nitrosamines in Cigarette Smoke. 43rd TOB. CHEM. RES. CONF., Richmond VA: Paper No. 45.

Caldwell WS and Conner JM (1990), Artifact Formation during Smoke Trapping: An Improved Method for the Determination of *N*-Nitrosamines in Cigarette Smoke. J. ASSOC. OFF. ANAL. CHEM. *73:* 783-789.

Campbell JA (1936), The Effects of Exhaust Gases from Internal Combustion Engines and of Tobacco Smoke upon Mice, with Special Reference to the Incidence of Tumors of the Lung. BRIT. J. EXP. PATHOL. *17:* 146-158.

Campbell JA (1937), Cancer of the Skin and Increase in Incidence of Primary Tumours of the Lung in Mice Exposed to Dust from Tarred Roads. BRIT. J. EXP. PATHOL. *18:* 287-294.

Campbell JA (1939), Carcinogenic Agents Present in the Atmosphere and Incidence of Primary Tumours in Mice. BRIT. J. EXP. PATHOL. *20:* 122-132.

Campbell JM and Lindsey AJ (1956), Polycyclic Hydrocarbons Extracted from Tobacco: The Effect upon Total Quantities Found in Smoke. BRIT. J. CANCER *10:* 649-652.

Candeli A, Hoffmann D, and Wynder EL (1963), Unpublished data cited in Wynder EL and Hoffmann D (1964), Experimental Tobacco Carcinogenesis. ADV. CANCER RES. *8:* 249-453 (see 323-333) and in Wynder EL and Hoffmann D (1967), *Tobacco and Tobacco Smoke: Studies in Experimental Carcinogenesis*, Academic Press, New York NY (see 373-374, Table VIII-14).

Cardon SZ, Alvord ET, Rand HJ, and Hitchcock R (1956), 3,4-Benzpyrene in the Smoke of Cigarette Paper, Tobacco and Cigarettes. BRIT. J. CANCER *10:* 485-497.

Catcott EJ, McCammon CJ, and Kotin P (1958), Pulmonary Pathology in Dogs due to Air Pollution. J. AM. VET. ASSOC. *113:* 331-335.

Chortyk OT and Schlotzhauer WS (1973), Studies on the Pyrogenesis of Tobacco Smoke Constituents (A Review). BEITR. TABAKFORSCH. *7:* 165-178.

Chortyk OT and Schlotzhauer WS (1986), Modification of an Automatic Cigarette Smoking Machine for Sidestream Smoke Collection. TOB. SCI. *30:* 122-126.

Chortyk OT and Schlotzhauer WS (1989), The Contribution of Low-Tar Cigarettes to Environmental Tobacco Smoke. J. ANAL. TOXICOL. *13:* 129-134.

Cogbill EC and Hobbs ME (1957), The Transfer of Metallic Constituents to the Main-Stream Smoke. TOB. SCI. *1:* 68-73.

Coggins CRE, Ayres PH, *et al.* (1992), Fourteen-Day Inhalation Study in Rats, Using Aged and Diluted Sidestream Smoke from a Reference Cigarette. FUND. APPL. TOXICOL. *19:* 133-140.

Coggins CRE, Ayres PH, *et al.* (1993), Subchronic Inhalation Study in Rats, Using Aged and Diluted Sidestream Smoke from a Reference Cigarette. INHAL. TOXICOL. *5:* 77-96.

Cohen BI, Raicht RF, and Fazzini E (1982), Reduction of *N*-Methyl-*N*-nitrosourea-Induced Colon Tumors in the Rat by Cholesterol. CANCER RES. *42:* 5050-5052.

Cohen D (1965), Epidemiologic Studies of Lung Cancer in Dogs. INTERNAT CONF. ON LUNG TUMOURS IN ANIMALS, Perugia, Italy (June 24-29).

Cohen JB and Bachman JD (1978), In Walker EA, Castegnaro M, Griciute L, and Lyle RE (Editors), *Environ-mental Aspects of* N-*Nitroso Compounds*, IARC, Lyon, France, IARC SCI. PUBL. NO. 19: 357-372.

Cohen LA (1987), Diet and Cancer. SCI. AM. *257:* 42-48.

Coker HA, Thomas AE, and Akintonwa A (1991a), Determination of the Total Level of Nitrosamines in Select Consumer Products in the Lagor Area of Nigeria. BULL. ENVIRON. CONTAM. TOXICOL. *47:* 706-710.

Coker HA, Thomas AE, Akintonwa A, and Odusote MO (1991b), Determination of the Total Level of Nitrosamines in Select Consumer Products in the Major Metropolitan Regions of Nigeria. INTERNAT. J. ENVIRON. ANAL. CHEM. *44:* 203-207.

Collman GW, Lundgren K, Shore D, Thompson CL, and Lucier GW (1986), Effects of α-Naphthoflavone on Levels of Sister Chromatid Exchange in Lymphocytes from Active and Passive Smokers: Dose-Response Relationships. CANCER RES. *46:* 6452-6455.

Cook JW (1957), Chemical Carcinogens and Their Significance. LANCET *1957 (i):* 333-335.

Cook JW (1961), Tobacco and Lung Cancer. ROYAL INST. CHEM. LECTURE SER. *1961 (5):* 1-18.

Cook JW, Hewett CL, and Hieger I (1932), Coal-Tar Constituents and Cancer. NATURE *130:* 926.

Cook JW, Hewett CL, and Hieger I (1933), Isolation of Cancer-Producing Hydrocarbons from Coal Tar. II. Isolation of 1,2- and 4,5-

Benzopyrenes, Perylene, and 1,2-Benzanthracene. J. CHEM. SOC. 395-398.

Cooper RL, Gilbert JAS, and Lindsey AJ (1955), Polycyclic Hydrocarbons in Cigarette Smoke: The Contribution Made by the Paper. BRIT. J. CANCER *9:* 442-445.

Crabtree HG (1946). Some Effects of Aromatic Hydrocarbons on Sulfur Metabolism and Tumor Induction in Mice. CANCER RES. *6:* 553-559.

Crabtree HG (1947). Anticarcinogenesis. BRIT. MED. BULL. *4:* 345-348.

Craddock VM (1990), Nitrosamines, Food and Cancer: Assessment. FOOD CHEM. TOXICOL. *28:* 63-66.

Crosby NT, Foreman JK, Palframan JF, and Sawyer P (1972), NATURE *238:* 342.

Cross CK and Bharucha KD (1979), J. AGR. FOOD CHEM. *27:* 1358-1360.

Dalbey WE, Nettesheim P, Griesemer R, Caton JE, and Guerin MR (1980), Chronic Inhalation of Cigarette Smoke by F344 Rats. J. NATL. CANCER INST. *64:* 383-390.

Dalhamn T (1961), Studies on the Effect of Sulfur Dioxide on Ciliary Activity *in vivo* and *in vitro* and on the Resorptional Capacity of the Nasal Cavity. AM. REV. RESP. DIS. *83:* 566-567.

Dalhamn T, Edfors ML, and Rylander R (1968a), Mouth Absorption of Various Compounds in Cigarette Smoke. ARCH. ENVIRON. HLTH. *16:* 831-835.

Dalhamn T, Edfors ML, and Rylander R (1968b), Retention of Cigarette Smoke Components in Human Lungs. ARCH. ENVIRON. HLTH. *17:* 746-748.

Dalhamn T and Rylander R (1964), Ciliastatic Action of Smoke from Filter-Tipped and Non-Tipped Cigarettes. NATURE *201:* 401-402.

Dalhamn T and Rylander R (1965), Ciliastasis and Cigarette Smoke: Varying Exposure Time. ARCH. OTOLARYNGOL. *81:* 379-382.

Dalhamn T and Sjoholm J (1963), Studies on $SO_2$, $NO_2$, and $NH_3$: Effect on Ciliary Activity in Rabbit Trachea of Single *in vitro* Exposure and Resorption in Rabbit Nasal Cavity. ACTA PHYSIOL. SCAND. *58:* 287-291.

Danish Institute of Protein Chemistry (1980), *Investigations on Formation and Occurrence of Volatile* N-*Nitrosamines in Danish Cheese.*

Davis BR, Whitehead JK, Gill ME, Lee PN, Butterworth AD, and Roe FJC (1975), Response of Rat Lung to Inhaled Vapour Phase Constituents (VP) of Tobacco Smoke Alone or in Conjunction with Smoke Condensate of Fractions of Smoke Condensate Given by Intratracheal Instillation. BRIT. J. CANCER *31:* 462-468.

DeMarini DM (1984), Genotoxicity of Tobacco Smoke and Tobacco Smoke Condensate. MUTATION RES. *114:* 59-89.

Dennis M, Cripps G, Tricker AR, Massey R, and McWeeny D (1984), *N*-Nitroso Compounds and Polycyclic Aromatic Hydrocarbons in Icelandic Smoke-Cured Mutton. FOOD CHEM. TOXICOL. *22:* 305-306.

Deutsch-Wenzel RP, Brune H, Grimmer G, Dettbarn G, and Misfeld J (1983), Experimental Studies in Rat Lungs on the Carcinogenicity and Dose Response Relationships of Eight Frequently Occurring Environmental Polycyclic Aromatic Hydrocarbons. J. NATL. CANCER INST. *71:* 539-543.

DiGiovanni J, Slaga TJ, Berry DL, and Juchau MR (1980), Inhibitory Effects of Environmental Chemicals on Polycyclic Aromatic Hydrocarbon Carcinogenesis. In Slaga TJ (Editor), *Carcinogenesis. A Comprehensive Survey. Vol. 5*, Raven Press, New York NY: 145-168.

Dipple A, Moschel RC, and Bigger CAH (1984), Polynuclear Hydrocarbons. In Searle CE (Editor), *Chemical Carcinogens, Second Edition*, AM. CHEM. SOC. MONOGRAPH 182, American Chemical Society, Washington DC: 41-163.

Dobrowolskaia-Zavadskaia N (1938), Doses of 1,2,5,6-Dibenzanthracene Capable of Producing Cancer in Mice. COMPT. REND. SOC. BIOL. *129:* 1055-105?.

Dontenwill W (1974), Tumorigenic Effects of Chronic Cigarette Smoke Inhalation on Syrian Golden Hamsters. In Karbe E and Park JF (Editors), *Experimental Lung Cancer: Carcinogenesis and Bioassays*, Springer, New York NY: 331-359.

Dontenwill W and Mohr U (1962), Experimental Studies on the Origin of Respiratory Tract Carcinoma. II. The Effect of Tobacco Smoke Condensate and Cigarette Smoke on the Golden Hamster Lung. Z. KREBSFORSCH. *65:* 62-68.

Doolittle DJ, Lee CK, Burger GT, and Hayes AW (1989), Comparative Studies on the Genotoxic Activity of Sidestream Smoke Condensate from Cigarettes Which Burn or Only Heat Tobacco. ENVIRON. MOLECUL. MUTAGENESIS Abstr. *#144:* 52.

Doolittle DJ, Lee CK, Ivett JL, *et al.* (1990), Comparative Studies on the Genotoxic Activity of Mainstream Smoke Condensate from Cigarettes Which Burn or Only Heat Tobacco. ENVIRON. MOLECUL. MUTAGENESIS *15:* 93-105.

Dorland I and (Newman WA), Taylor EJ (Editor) (1988). *27th Edition, Dorland's Illustrated Medical Dictionary*. WB Saunders Company, Philadelphia PA.

Druckrey H (1961), Experimental Investigations on the Possible Carcinogenic Effects Of Tobacco Smoking. ACTA MED. SCAND. SUPPL. *369:* 24-42.

Druckrey H, Landschütz C, and Preussmann R (1968), Z. KREBSFORSCH. *71:* 135-139.

Druckrey H and Preussmann R (1962), Zur Entstehung carcinogener Nitrosamine am Beispiel des Tabaksrauch. NATURWISSENSCHAFT. *49:* 498-499.

Druckrey H, Preussmann R, Ivankovic S, and Schmähl D (1967), Organotrope carcinogene Wirkungen bei 65 verschiedenen *N*-Nitroso-Verbindungen an BD-Ratten. Z. KREBSFORSCH. *69:* 103-201.

Druckrey H, Preussmann R, Schmähl D, and Müller M (1961), Chemische Konstitution und carcinogene Wirkung bei Nitrosamines. NATURWISSENSCHAFT. *48:* 134-135.

Ducos P and Gaudin R (1986), Occupational Exposure to Volatile Nitrosamines in the Rubber Industry in France. CAH NOTES DOC. *123:* 145-150.

Dunn BP and Stich HF (1984), Determination of Free and Protein-Bound *N*-Nitrosoproline in Nitrite-Cured Meat Products. FOOD CHEM. TOXICOL. *22:* 609-614.

Eatough DJ, Benner CL, Bayona JM, Richards G, Lamb JD, Lee ML, Lewis EA, and Hansen LD (1989), Chemical Composition of Environmental Tobacco Smoke. 1. Gas-Phase Acids and Bases. ENVIRON. SCI. TECHNOL. *23:* 679-687.

Eatough DJ, Hansen LD, and Lewis EA (1990a), The Chemical Characterization of Environmental Tobacco Smoke. In Ecobichon DJ and Wu JM (Editors), *Environmental Tobacco Smoke*. Proc. Internat. Symp. at McGill University, 1989, Lexington Books, D.C. Heath and Company, Lexington MA: 3-39.

Eatough DJ, Hansen LD, and Lewis EA (1990b), The Chemical Characterization of Environmental Tobacco Smoke. ENVIRON. TECH. *11:* 1071-1085.

Egan H, Preussmann R, O'Neill IK, Eisenbrand G, Spiegelhalder B, and Bartsch H (Editors) (1983), *Environmental Carcinogens, Selected Methods of Analysis. Vol. 6:* N-*Nitroso Compounds*. IARC, Lyon, France, IARC SCI. PUBL. NO. 45.

Einistoe P and Sorsa M (1985), Mutagenic Activity in Urine of Active and Passive Smokers. MUTATION RES. *147:* 292.

Eisenbrand G (1981), N-*Nitrosoverbindungen in Nahrung und Umwelt*. Wiss. Verlagsgesellschaft, Stuttgart, Germany.

Eisenbrand G, Archer M, Brunnemann KD, Fine DH, Hecht SS, Hoffmann D, Krull J, and Webb KS (1983), Problems of Contamination and Artefact Formation in Nitrosamine Sampling and Analysis. In Egan H, Preussmann R, Eisenbrand G, Spiegelhalder T, O'Neill IK, and Bartsch H (Editors), *Environmental Carcinogens. Selected Methods of Analysis. Vol. 6:* N-*Nitroso Compounds*. IARC, Lyon, France, IARC SCI. PUBL. NO. 45: 25-34.

Eisenbrand G, Blankart M, Sommer H, and Weber B (1991), *N*-Nitrosoalkanolamines in Cosmetics. In O'Neill IK, Chen J, and Bartsch H (Editors), *Relevance to Human Cancer of* N-*Nitroso Compounds, Tobacco Smoke, and Mycotoxins*, IARC, Lyon, France. IARC SCI. PUBL. NO. 105: 238-241.

Eisenbrand G, Spiegelhalder B, Janzowski C, and Preussmann R (1978), Volatile and Nonvolatile *N*-Nitroso Compounds in Foods and Other Environmental Media. In Walker EA, Castegnaro M, Griciute L, and Lyle RE (Editors), *Environmental Aspects of* N-*Nitroso Compounds*, IARC, Lyon, France, IARC SCI. PUBL. NO. 19: 311-324.

Elgersma RHC, Sen RP, Stephany RW, Schuller PL, Webb KS,and Gough TA (1978), NETH. MILK DAIRY J. *32:* 125-142.

Ellen G (1990), Exposure to Preformed *N*-Nitroso Compounds. DRUG DEV. EVAL. *16:* 119-146.

Environmental Protection Agency (1981), *Maleic Hydrazide: Notification of Issuances of Notice of Intent to Suspend Pesticide Registration*. FED. REG. *46 (No. 179)*: 46000.

Environmental Protection Agency (1989), *Exposures Factor Handbook*. EPA/600/8-89/043.

Environmental Protection Agency (1990a), *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children*. Draft Document EPA/600/6-90/006A (May 1990).

Environmental Protection Agency (1990b), *Environmental Tobacco Smoke: A Guide to Workplace Smoking Policies*. Draft Document EPA/400/6-90/004 (June 25, 1990).

Environmental Protection Agency (1990c), *Technical Support Document for the 1990 Citizens Guide to Radon*. EPA, Office of Radiation Programs, Radon Division, Washington DC (August 16).

Environmental Protection Agency (1992), *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders* (December 1992).

Epstein SS, Andrea JJ, Forsyth J, and Mantel N (1967), The Null Effect of Antioxidants on the Carcinogenicity of 3,4,9,10-Dibenzpyrene to Mice. LIFE SCI. *6:* 225-233.

Erickson M, Lakings D, Drinkwine A, and Spigarelli J (1985), Quantitative Analysis of *N*-Nitrosodiethanolamine by High Performance Liquid Chromatography Thermal Energy Analyzer Detection. J. SOC. COSMET. CHEM. *36:* 213-222.

Essenberg JM (1952), Cigarette Smoke and the Incidence of Primary Neoplasm of the Lung in the Albino Mouse. SCIENCE *116:* 561-562.

Essenberg JM (1954a), Incidence of Lung Tumors in Albino Mice Exposed to Smoke from Cigarette Paper. SCIENCE *120:* 1000.

Essenberg JM (1954b), Effect of Cigarette Smoke on Lung Tumors of Laboratory Animals. J. AM. MED. ASSOC. *156:* 909.

Essenberg JM (1957), Further Study of Tumor Formation in the Lungs of Albino Mice. WEST. J. SURG. OBST. GYNECOL. *65:* 161-163.

Essenberg JM, Horowitz M, and Gaffney F (1955), The Incidence of Lung Tumors in Albino Mice Exposed to the Smoke from Cigarettes Low in Nicotine Content. WEST. J. SURG. OBST. GYNECOL. *63:* 265-267.

Essenberg JM, Leavitt AM, and Gaffney E (1956), The Effect of Arsenic in Tobacco on Primary Neoplasms of the Lungs of Albino Mice. WEST. J. SURG. OBST. GYNECOL. *64:* 35-36.

Eudy LW, Thome FA, Heavner DL, Green CR, and Ingebrethsen BJ (1985), Studies of the Vapor-Particulate Distribution of Environmental Nicotine by Selected Trapping and Detection Methods. 39th TOB. CHEM. RES. CONF., Montreal PQ, Canada: Paper No. 38.

Falk HL, Kotin P, and Thompson S (1964), Inhibition of Carcinogenesis. The Effect of Hydrocarbons and Related Compounds. ARCH. ENVIRON. HLTH. *9:* 169-179.

Fan TY, Goff V, Song L, Fine DH, Arsenault GP, and Biemann K (1977), *N*-Nitrosodiethanolamine in Cosmetics, Lotions and Shampoos. FOOD COSMET. TOXICOL. *15:* 423-430.

Farland W, Bayard S, and Jinot J (1994), Environmental Tobacco Smoke: A Public Health Conspiracy? A Dissenting View. J. CLIN. EPIDEMIOL. *47:* 335-337.

Fay JR, Perry LR, Kanerva LA, Sigman CC, and Helmes CT (1985), Inhibitors of Chemical Carcinogenesis. Document prepared in 1984, revised in 1985 for Sci. Coordinator Environ. Cancer, NCI, Bethesda MD.

Fazio T, Havery DC, and Howard JW (1982), In Bartsch H, O'Neill IK, Castegnaro M. and Okada M (Editors), N-*Nitroso Compounds: Occurrence and Biological Effects*, IARC, Lyon, France, IARC SCI. PUBL. NO. 41.

Felton KS and Knize MG (1990), Heterocyclic Amine Mutagens/Carcinogens in Foods. In Cooper CS and Grover PL (Editors), *Chemical Mutagenesis and Carcinogenesis*, Springer-Verlag, Berlin/Heidelberg: 471-502.

Fiala ES, Bobotas G, Kulakis C, Wattenberg LW, and Weissburger JH (1977), The Effect of Disulfiram and Related Compounds on the *in vivo*

Metabolism of the Colon Carcinogen 1,2-Dimethylhydrazine. BIOCHEM. PHARMACOL. *26:* 1763-1768.

Fiddler W, Pensabene JW, Doerr RC, and Wasserman AE (1972), Formation of *N*-Nitrosodimethylamine from Naturally Occurring Quaternary Ammonium Compounds and Tertiary Amines. NATURE *236:* 307.

Fieser LF (1957), Chemical Carcinogenesis. ARTHUR STOLLE FESTSCHRIFFTE 489-498.

Fine DH (1983), HPLC-TEA Determination of NDELA and Similar Compounds in Cosmetics. In Egan H, Preussmann R, Eisenbrand G, Spiegelhalder T, O'Neill IK, and Bartsch H (Editors), *Environmental Carcinogens. Selected Methods of Analysis. Vol. 6:* N-*Nitroso Compounds*. IARC, Lyon, France, IARC SCI. PUBL. NO. 45: 309-317.

Fine DH, Rounbehler DP, Sawicki E, and Krost K (1977a), Determination of Dimethylnitrosamine in Air and Water by Thermal Energy Analysis: Validation of Analytical Procedures. ENVIRON. SCI. TECHNOL. *11:* 577-580.

Fine DH, Rounbehler DP, Rounbehler A, Silvergleid A, Sawicki E, Krost K, and de Marais GA (1977b), Determination of Dimethylnitrosamine in Air, Water and Soil by Thermal Energy Analysis. ENVIRON. SCI. TECHNOL. *11:* 581-584.

Fischer S, Castonguay A, Kaiserman M, Spiegelhalder B, and Preussmann R (1990a), Tobacco-Specific Nitrosamines in Canadian Cigarettes. J. CANCER RES. CLIN. ONCOL. 563-568.

Fischer S and Spiegelhalder B (1989), Improved Method for the Determination of Tobacco-Specific Nitrosamines (TSNA) in Tobacco Smoke. BEITR. TABAKFORSCH. INTERNAT. *14:* 145-153.

Fischer S, Spiegelhalder B, Eisenbarth J, and Preussmann R (1990b), Investigations on the Origin of Tobacco-Specific Nitrosamines in Mainstream Smoke of Cigarettes. CARCINOGENESIS *11:* 723-730.

Fischer S, Spiegelhalder B, and Preussmann R (1989a), Tobacco-Specific Nitrosamines in Mainstream Smoke of West German Cigarettes — Tar Alone Is Not a Sufficient Index for the Carcinogenic Potential of Cigarettes. CARCINOGENESIS *10:* 169-173.

Fischer S, Spiegelhalder B, and Preussmann R (1989b), Influence of Smoking Parameters on the Delivery of Tobacco-Specific Nitrosamines in Cigarette Smoke — A Contribution to Relative Risk Evaluation. CARCINOGENESIS *10:* 1059-1066.

Fischer S, Spiegelhalder B, and Preussmann R (1989c), Preformed Tobacco-Specific Nitrosamines in Tobacco: Role of Nitrate and Influence of Tobacco Type. CARCINOGENESIS *10:* 1511-1517.

Fischer S, Spiegelhalder B, and Preussmann R (1990c), Tobacco-Specific Nitrosamines in European and USA Cigarettes. ARCH. GESCHWULSTFORSCH. *60:* 169-177.

Fischer S, Spiegelhalder B, and Preussmann R (1990d), Tobacco-Specific Nitrosamines in the Mainstream Smoke of German Cigarettes: Condensate Content Does Not Suffice as the Sole Harmful Substance Parameter. LEBENSM. CHEM. *44:* 50-52.

Fischer S, Spiegelhalder B, and Preussmann R (1991a), No Pyrosynthesis of *N'*-Nitrosonornicotine (NNN) and 4-(*N*-methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) from Nicotine. In Adlkofer F and Thurau K (Editors), *Effects of Nicotine on Biological Systems*, Birkhauser Verlag, Boston MA: 103-107.

Fischer S, Spiegelhalder B, and Preussmann R (1991b), Tobacco-Specific Nitrosamines in Commercial Cigarettes: Possibilities for Reducing Exposure. In O'Neill IK, Chen J, and Bartsch H (Editors), *Relevance to Human Cancer of* N-*Nitroso Compounds, Tobacco Smoke, and Mycotoxins*, IARC, Lyon, France. IARC SCI. PUBL. NO. 105: 489-492.

Fong YY and Chan WC (1973), FOOD COSMET. TOXICOL. *11:* 841-845.

Fong YY and Chan WC (1976), FOOD COSMET. TOXICOL. *14:* 95-98.

Fontham ET, Correa P, Wu-Williams A, Reynolds P, Greenberg RS, Buffler PA, Chen VW, Boyd P, Alterman T, Austin DF, Liff J, and Greenberg SD (1991), Lung Cancer in Nonsmoking Women: A Multicenter Case-Control Study. CANCER EPIDEMIOL. BIOMARKERS PREVENT. *1:* 35-43.

Fredrickson JD (1965/1967), Personal communication on R.J. Reynolds Tobacco Company R&D project entitled *Study of Burley Tobacco Smoke Condensate.*

Goff EV and Fine DH (1979), Analysis of Volatile *N*-Nitrosamines in Alcohol Beverages. FOOD COSMET. TOXICOL. *17:* 569-573.

Goodhead K, Gough TA, Webb KS, Stadhouders J, and Elgersma RHC (1976), NETH. MILK DAIRY *30:* 207-221.

Gori GB (Editor) (1976a), *Report No. 1. Toward Less Hazardous Cigarettes. The First Set of Experimental Cigarettes.* DHEW Publ. No. (NIH) **76-905.**

Gori GB (Editor) (1976b), *Report No. 2. Toward Less Hazardous Cigarettes. The Second Set of Experimental Cigarettes.* DHEW Publ. No. **(NIH) 76-1111.**

Gori GB (Editor) (1977), *Report No. 3. Toward Less Hazardous Cigarettes. The Third Set of Experimental Cigarettes.* DHEW Publ. No. (NIH) **77-1280.**

Gori GB (Editor) (1980), *Report No. 4. Toward Less Hazardous Cigarettes. The Fourth Set of Experimental Cigarettes.* DHEW Publ. (NIH) **March (1980).**

Gori GB (1994a), Science, Policy, and Ethics: The Case of Environmental Tobacco Smoke. J. CLIN. EPIDEMIOL. *47:* 325-334.

Gori GB (1994b), Response: Reply to the Preceding Dissents [of Farland W *et al.* (1994) and Jinot J and Byarad S (1994)]. J. CLIN. EPIDEMIOL. *47:* 351-353.

Gori GB and Bock FG (Editors) (1980), *A Safe Cigarette?* Banbury Report 3, Cold Spring Harbor Laboratory, Cold Spring Harbor NY.

Gori GB and Mantel N (1991), Mainstream and Environmental Tobacco Smoke. REGUL. TOXICOL. PHARMACOL. *14:* 88-105.

Gottschalk RG (1942), Tumor Production in Mice by Benzpyrene. PROC. SOC. EXPTL. BIOL. MED. *50:* 369-373.

Gough TA (1977), GUT *18:* 301-302.

Gough TA, McPhail MG, Webb KS, Wood BJ, and Coleman RF (1977), J. SCI. FOOD. AGR. *28:* 345-351.

Gough TA, Webb KS, and Coleman RF (1978), Estimate of the Volatile Nitrosamine Content of UK Food. NATURE *272:* 161-163.

Graham EA, Croninger AB, and Wynder EL (1957), Experimental Production of Carcinoma with Cigarette Tar. IV. Successful Experiments with Rabbits. PROC. AM. ASSOC. CANCER RES. *2(3):* 208.

Grasso P (1984), Carcinogens in Food. Chapter 19 in Searle CE (Editor), *Chemical Carcinogens. Second Edition*, **American Chemical Society Monograph 182**, American Chemical Society, Washington DC: 1205-1239.

Gray JI (1982), In Scanlan RA and Tannenbaum SR (Editors), N-*Nitroso Compounds*, **Am. Chem.Soc. Symp. Series No. 174**, American Chemical Society, Washington DC.

Gray JI and Randall CJ (1979), J. FOOD PROT. *42:* 168-179.

Green CR (1980), Personal communication.

Green CR (1990), A Discussion of Smoke Generation and Analytical Procedure in 'The Contribution of Low Tar Cigarettes to Environmental Tobacco Smoke.' J. ANAL. TOXICOL. *14:* 261.

Griffin HR, Hocking MB, and Lowery DG (1975), Arsenic Determination in Tobacco by Atomic Absorption Spectrometry. ANAL. CHEM. *47:* 229-233.

Grimmer G, Böhnke H, and Harke HP (1977a), Passive Smoking: Measurement of Concentration of Polycyclic Aromatic Hydrocarbons in Rooms after Machine Smoking of Cigarettes. INTERNAT. ARCH. OCCUP. ENVIRON. HLTH. *40:* 83-92.

Grimmer G, Böhnke H, and Harke HP (1977b), Passive Smoking: Intake of Polycyclic Aromatic Hydrocarbons by Breathing of Cigarette Smoke-Containing Air. INTERNAT. ARCH. OCCUP. ENVIRON. HLTH. *40:* 93-99.

Grimmer G, Brune H, Dettbarn G, Jacob J, Misfeld J, Mohr, Naujack KW, Timm J, and Wenzel-Hartung R (1991), Relevance of Polycyclic Aromatic Hydrocarbons as Environmental Carcinogens. FRESENIUS J. ANAL. CHEM. *339:* 792-795.

Grimmer G, Brune H, Dettbarn G, Naujack KW, Mohr U, and Wenzel-Hartung R (1988), Contribution of Polycyclic Aromatic Hydrocarbons to the Carcinogenicity of Sidestream Smoke of Cigarettes Evaluated by Implantation into the Lung of Rats. CANCER LETT. *43:* 173-177.

Grimmer G, Naujack KW, and Dettbarn G (1986), Gas Chromatographic Determination of Polycyclic Aromatic Hydrocarbons, Aza-Arenes, Aromatic Amines in the Particle and Vapor Phase of Mainstream and Sidestream Smoke of Cigarettes. INTERNAT. EXPTL. TOXICOL. SYMP. ON PASSIVE SMOKING, Essen FRG.

Grimmer G, Naujack KW, and Dettbarn G (1987), Gas Chromatographic Determination of Polycyclic Aromatic Hydrocarbons, Aza-Arenes, Aromatic Amines in the Particle and Vapor Phase of Mainstream and Sidestream Smoke of Cigarettes. TOXICOL. LETT. *35:* 117-124.

Gritsiute LA and Mironova AJ (1960), The Carcinogenic Action of Tobacco Tar. VOPROSY ONKOL. *6:* 25-33.

Guerin M (1959), Pulmonary Tumors and Buccal Cancer in the Rat Exposed to the Inhalation of Cigarette Smoke. BULL. ASSOC. FRANC. ÉTUDE CANCER *46:* 295-309.

Guerin MR, Jenkins RA, and Tomkins BA (1992), *The Chemistry of Environmental Tobacco Smoke: Composition and Measurement.* Lewis Publishers, Boca Raton FL.

Guillerm R, Badré R, and Vignon B (1961), Effets Inhibiteurs de la Fumée de Tabac sur l'Activité Ciliare de l'Épithélium Respiratoire et Nature des Composants Responsables. BULL. ACAD. NAT. MED. (FRANCE) 416-423.

Gwynn RH (1954), Studies on Promotion of Tumour Development (Co-Carcinogenesis). BRIT. EMP. CANCER CAMP., ANN. RPT. *32:* 171-172.

Gwynn RH and Salaman MH 1956), Tests of Tobacco Products for Tumour Initiation and Promotion in Mouse Skin. BRIT. EMP. CANCER CAMP., ANN. RPT. *34:* 279.

Habs M, Preussmann R, and Schmähl D (1981), Dose Response Study on the Carcinogenicity of *N*-Nitrosodiethanolamine (NDELA) in Male Sprague Dawley Rats. J. CANCER RES. CLIN. ONCOL. *99:* A27.

Hamburg A and Hamburg A (1982), Formation of *N*-Nitrosoproline in Some Meat Products during Technological Treatment. TR. TALLIN POLITEKH INST. *537:* 57-63.

Hamburg A and Kann J (1982), Method for Determining *N*-Nitrososarcosine (NSAR) and Its Content in Food Products. TR. TALLIN POLITEKH INST. *537:* 43-55.

Hamer D and Woodhouse DL (1956), Biological Tests for Carcinogenic Action of Tar from Cigarette Smoke. BRIT. J. CANCER *10:* 49-53.

Hammond EC and Machle D (1956), In Mayer and Maier (Editors), *Pulmonary Carcinoma*, JB Lippincott.

Hansen T, Iwaoka W, Green L, and Tannenbaum SR (1977), Analysis of *N*-Nitrosoproline in Raw Bacon. Further Evidence that Nitrosoproline Is Not a Major Precursor of *N*-Nitrosopyrrolidine. J. AGR. FOOD CHEM. *25:* 1423-1426.

Harley NH, Cohen BS, and Tso TC (1980), Polonium-210. A Questionable Risk Factor in Smoking-Related Carcinogenesis. In Gori GB and Bock FG (Editors), *A Safe Cigarette?* Banbury Report 3, Cold Spring Harbor Laboratory, Cold Spring Harbor NY: 93-104.

Harris RJC, Negroni G, Ludgate S, *et al.* (1974), The Incidence of Lung Tumours in C57BL Mice Exposed to Cigarette Smoke:Air Mixtures for Prolonged Periods. INTERNAT. J. CANCER *14:* 130-136.

Hartwell JL (1951), *Survey of Compounds Which Have Been Tested for Carcinogenic Activity.* USPHS Publ. No. 149, 2nd Edition, Washington DC.

Hattemeyer-Frey HA and Travis CC (1991), Benzo-a-pyrene: Environmental Partitioning and Human Exposure. TOXICOL. IND. HLTH. *7:* 141-157.

Havery DC and Fazio T (1977), J. ASSOC. OFF. ANAL. CHEM. *60:* 517-519.

Havery DC, Fazio T, and Howard JW (1978), Trends in Levels of *N*-Nitrosopyrrolidine in Fried Bacon. J. ASSOC. OFF. ANAL. CHEM. *61:* 1379-1382.

Havery DC, Hotchkiss JH, and Fazio T (1981), Nitrosamines in Malt and Malt Beverages. J. FOOD SCI. *46:* 501-505.

Havery DC, Hotchkiss JH, and Fazio T (1982), Rapid Determination of Volatile Nitrosamines in Nonfat Dry Milk. J. DAIRY SCI. *65:* 182-185.

Havery DC, Kline DA, Miletta EM, Joe FL, and Fazio T (1976), J. ASSOC. OFF. ANAL. CHEM. *59:* 540-546.

Hecht SS, Bondinell WE, and Hoffmann D (1973), Isolation and Identification of Alkylchrysenes in Cigarette Smoke. 27th TOB. CHEM. RES. CONF., Winston-Salem NC: Paper No. 32.

Hecht SS, Bondinell WE, and Hoffmann D (1974), Chrysene and Methylchrysenes: Presence in Tobacco Smoke and Carcinogenicity. J. NATL. CANCER INST. *53:* 1121-1133.

Hecht SS, Chen CB, Dong M, Ornaf RM, Hoffmann D, and Tso TC (1977a), Studies on Non-Volatile Nitrosamines in Tobacco. BEITR. TABAKFORSCH. INTERNAT. *9:* 1-6.

Hecht SS, Chen CB, Hirota N, Ornaf RM, Tso TC, and Hoffmann D (1978a), Tobacco Specific Nitrosamines: Formation from Nicotine *in vitro* and During Curing of Tobacco and Carcinogenicity in Strain-A Mice. J. NATL. CANCER INST. *60:* 819-824.

Hecht SS, Chen CB, and Hoffmann D (1976a), TETRAHEDRON LETT. *8:* 593.

Hecht SS and Hoffmann D (1991b), 4-(*N*-Methylnitrosamino)-1-(3-pyridyl)-1-butanone, a Nicotine-Derived Tobacco-Specific Nitrosamine, and Cancer of the Lung and Pancreas in Humans. In Brugge J, Curran T, Harlow E, and McCormick F (Editors), *The Origins of Human Cancer: A Comprehensive Review*, Cold Spring Harbor Laboratory, Cold Spring Harbor NY: 745-755.

Hecht SS, Loy M, Maronpot R, and Hoffmann D (1976c), A Study of Chemical Carcinogenesis: Comparative Carcinogenicity of 5-Methylchrysene, Benzo[*a*]pyrene, and Modified Chrysenes. CANCER LETT. *1:* 147-154.

Hecht SS, Ornaf RM, Dong M, and Hoffmann D (1976b), Studies on Nonvolatile Nitrosamines in Tobacco. 30th TOB. CHEM. RES. CONF., Nashville TN: Paper No. 27.

Hecht SS, Ornaf RM, and Hoffmann D (1974a), *N*-Nitrosoalkaloids in Tobacco. 28th TOB. CHEM. RES. CONF., Raleigh NC: Paper No. 36.

Hecht SS, Ornaf RM, and Hoffmann D (1975b), Chemical Studies on Tobacco Smoke. XXXIII. *N'*-Nitrosonornicotine in Tobacco: Analysis of Possible Contributing Factors and Biological Implications. J. NATL. CANCER INST. *54:* 1237-1244.

Hecht SS, Thorne RL, and Hoffmann D (1974c), Studies on Tumor Promoters in Tobacco Smoke. 28th TOB. CHEM. RES. CONF., Raleigh NC: Paper No. 42.

Hecht SS, Thorne RL, Maronpot R, and Hoffmann D (1975), Tumor Promoting Subfractions of the Weakly Acidic Fraction. J. NATL. CANCER INST. *55:* 1329-1336.

Hedler L and Marquardt P (1968), Occurrence of Diethylnitrosamine in Some Samples of Food. FOOD COSMET. TOXICOL. *6:* 341.

Helgason T, Ewen S, Jaffray B, Stowers J, Outram J, and Pollock J (1984), *N*-Nitrosamines in Smoked Meats and Their Relation to Diabetes. In O'Neill IK, von Borstel RC, Miller CT, Long J, and Bartsch H (Editors), N-*Nitroso Compounds: Occurrence, Biological Effects and Relationship to Human Cancer,* IARC, Lyon, France, IARC SCI. PUBL. NO. 57: 911-920.

Henry CJ and Kouri RE (1984), *Chronic Exposure of Mice to Cigarette Smoke. Final Report On "Smoke Inhalation in Mice."* Field, Rich and Associates, New York NY.

Henry CJ and Kouri RE (1986), Chronic Inhalation Studies in Mice. II. Effects of Long-Term Exposure to 2R1 Cigarette Smoke on (C57BL/Cum x C3H/Anf/Cum)F1 Mice. J. NATL. CANCER INST. *77:* 203-212.

Hiller FC, Anderson PI, and Mazumber MK (1987), Deposition of Sidestream Cigarette Smoke in the Human Respiratory Tract. II. Deposition of Ultrafine Smoke Particles. TOXICOL. LETT. *35:* 95-99.

Hiller FC, Mazumder MK, Wilson JD, McLeod PC, and Bone RC (1982a), Human Respiratory Tract Deposition Using Multimodal Aerosols. J. AEROSOL SCI. *13:* 337-343.

Hiller FC, McCusker KT, Mazumder MK, Wilson JD, and Bone RC (1982b), Deposition of Sidestream Cigarette Smoke in the Human Respiratory Tract. AM. REV. RESP. DIS. *125:* 406-408.

Hoffman HE and Griffin AC (1958), Action of Cigarette Tar and Smoke on Chemically Induced Carcinogenesis. TEXAS RPT. BIOL. MED. *16:* 333-345.

Hoffmann D, Adams JD, and Brunnemann KD (1987), A Critical Look at *N*-Nitrosamines in Environmental Tobacco Smoke. TOXICOL. LETT. *35:* 1-8.

Hoffmann D, Brunnemann KD, Adams JD, and Hecht SS (1984a), Formation and Analysis of *N*-Nitrosamines in Tobacco Products and Their Endogenous Formation in Consumers. In O'Neill IK, von Borstel RC, Miller CT, Long J, and Bartsch H (Editors), N-*Nitroso Compounds: Occurrence, Biological Effects and Relationship to Human Cancer,* IARC, Lyon, France, IARC SCI. PUBL. NO. 57: 743-762.

Hoffmann D, Brunnemann KD, Prokopczyk B, and Djordjevic MV (1994), Tobacco-Specific *N*-Nitrosamines and *Areca*-Derived *N*-Nitrosamines: Chemistry, Biochemistry, Carcinogenicity, and Relevance to Humans. J. TOXICOL. ENVIRON. HLTH. *41:* 1-52.

Hoffmann D, Haley NJ, Adams JD, and Brunnemann KD (1984b), Tobacco Sidestream Smoke: Uptake by Smokers. PREV. MED. *13:* 608-617.

Hoffmann D and Hecht SS (1990), Advances in Tobacco Carcinogenesis. Chapter 3 in Cooper CS and Grover P (Editors), *Chemical Carcinogenesis and Mutagenesis. I,* Springer-Verlag, London, UK: 63-102.

Hoffmann D, Hecht SS, Ornaf RM, Wynder EL, and Tso TC (1976b), Chemical Studies on Tobacco Smoke. XLII. Nitrosonornicotine: Presence in Tobacco, Formation and Carcinogenicity. In Walter EA, Bogovski P, and Griciute L (Editors), *Environmental* N-*Nitrosamines: Analysis and Formation.* IARC, Lyon, France, IARC SCI. PUBL. NO. 14: 307-320.

Hoffmann D, Masuda Y, and Wynder EL (1969a), α-Naphthylamine and β-Naphthylamine in Cigarette Smoke. NATURE. *221:* 254-256.

Hoffmann D, Rathkamp G, and Wynder EL (1969b), Chemical Studies on Tobacco Smoke. IX. Quantitative Analysis of Chlorinated Hydrocarbon Insecticides. BEITR. TABAKFORSCH. 5: 140-148.

Hoffmann D, Rivenson A, Chung FL, and Wynder EL (1993), Potential Inhibitors of Tobacco Carcinogenesis. In Diana JN and Pryor WA (Editors) (1993), *Tobacco Smoking and Nutrition: Influence of Nutrition on Tobacco-Associated Health Risks,* ANN. N.Y. ACAD. SCI. *686:* 140-160.

Hoffmann D and Wynder EL (1962), A Study of Air Pollution Carcinogens. II. The Isolation and Identification of Polynuclear Aromatic Hydrocarbons from Gasoline Engine Exhaust Condensate. CANCER *15:* 93-102.

Hoffmann D and Wynder EL (1963), Unpublished data cited in Wynder EL and Hoffmann D (1967), *Tobacco and Tobacco Smoke: Studies in Experimental Carcinogenesis.* Academic Press, New York NY: 530.

Hoffmann D and Wynder EL (1967), The Reduction of the Tumorigenicity of Cigarette Smoke Condensate by Addition of Sodium Nitrate to Cancer. CANCER RES. *27:* 172-174.

Hoffmann D and Wynder EL (1968), Selective Reduction of the Tumorigenicity of Tobacco Smoke. Experimental Approaches. In Wynder EL and Hoffmann D (Editors), *Toward a Less Harmful Cigarette.* NATL. CANCER INST. MONOGRAPH 28: 151-172.

Hoffmann D and Wynder EL (1970), Chamber Development and Aerosol Dispersion. In Hanna MJ, Nettesheim P, and Gilbert JR (Editors), *Inhalation Carcinogenesis,* US AEC Series *18:* 178.

Hoffmann D and Wynder EL (1972a), Selective Reduction of Tumorigenicity of Tobacco Smoke. II. Experimental Approaches. J. NATL. CANCER INST. *48:* 1855-1868.

Hoffmann D and Wynder EL (1972b), A Study of Tobacco Carcinogenesis. XV. Chemical Composition and Tumorigenicity of Tobacco Smoke. In Schmeltz I (Editor), *The Chemistry of Tobacco and Tobacco Smoke,* Plenum Publishing Co: 123-147.

Holcomb LC (1993), Indoor Air Quality and Environmental Tobacco Smoke: Concentration and Exposure. ENVIRON. INTERNAT. *19:* 9-40.

Holland RH, Kozlowski EJ, and Booker L (1963), The Effect of Cigarette Smoke on the Respiratory System of the Rabbit. A Final Report. CANCER *16:* 612-615.

Homburger F (1965), Les Rapports entre Tabac et Cancer: Pathologie Expérimentale. MÉD. HYG. *23:* 179-181.

Homburger F and Treger A (1960), PROG. EXPTL. TUMOR RES. *1:* 311-328.

Homburger F and Treger A (1965), Effects of Intravenous Carcinogen and Tobacco Condensate Injections upon the Incidence of Lung Tumors in A/He Mice. In Severi L (Editor), *Lung Tumors in Animals,* Division of Cancer Research, University of Perugia, Italy: 527-536.

Homburger F, Treger A, and Boger E (1968), Experimental Studies on the Inhibition of Carcinogenesis by Cigarette-Smoke Condensates and

Carcinogen-Related Substances. In Wynder EL and Hoffmann D (Editors), *Toward a Less Harmful Cigarette.* NATL. CANCER INST. MONOGRAPH 28: 259-270.

Homburger F, Treger A, and Boger E (1971), Inhibition of Murine Subcutaneous and Intravenous Benzopentaphene Carcinogenesis by Sweet Orange Oils and *D*-Limonene. ONCOLOGY *25:* 1-10.

Hotchkiss JH, Havery DC, and Fazio T (1981), Rapid Method for Estimation of *N*-Nitrosodimethylamine in Malt Beverages. J. ASSOC. OFF. ANAL. CHEM. *64:* 929-932.

Huang DP, Ho JHC, Webb KS, Wood BJ, and Gough TA'(1981), FOOD COSMET. TOXICOL. *19:* 167-171.

Huber GL (1989), Physical, Chemical, and Biological Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products. In Huber GL (Editor), *Tobacco and Smoking Cessation. I.* SEM. RESP. MED. *10:* 297-332.

Huber GL (1990), Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children. Document Submitted to the Environmental Protection Agency (September 28).

Huber GL, Brockie RE, and Mahajan VK (1992), Passive Smoking: How Great a Hazard? TOB. REPORTER *119 (5):* 36-38, 40, 42, 44,46.

Husgafvel-Pursiainen K, Sorsa M, Engstrom K, and Einistoe P (1987), Passive Smoking at Work: Biochemical and Biological Measures of Exposure to Environmental Tobacco Smoke. INT. ARCH. OCCUP. ENVIRON. HLTH. *59:* 337-345.

IARC (1972), 4-Aminobiphenyl. IARC, Lyon, France, IARC **Monograph 1:** 74-79.

IARC (1973), Nickel and Inorganic Nickel Compounds. IARC, Lyon, France, IARC **Monograph 3:** 126-149.

IARC (1974a), 2-Naphthylamine. IARC, Lyon, France, IARC **Monograph 4:** 97-111.

IARC (1974b), Hydrazine. IARC, Lyon, France, IARC **Monograph 4:** 127-136.

IARC (1974c), Benzene. IARC, Lyon, France, IARC **Monograph 7:** 203-211.

IARC (1979a), Acrylonitrile. IARC, Lyon, France, IARC **Monograph 19:** 73-113.

IARC (1979b), Vinyl Chloride. IARC, Lyon, France, IARC **Monograph 19:** 377-438.

IARC (1980a), Arsenic and Arsenic Compounds. IARC, Lyon, France, IARC **Monograph 23:** 39-141.

IARC (1980b), Chromium and Chromium Compounds. IARC, Lyon, France, IARC **Monograph 23:** 205-323.

IARC (1980c), Lead and Lead Compounds. IARC, Lyon, France, IARC **Monograph 23:** 325-415.

IARC (1982a), Formaldehyde. IARC, Lyon, France, IARC **Monograph [Suppl. 4]:** 131-132.

IARC (1982b), Benzene. IARC, Lyon, France, IARC **Monograph 29:** 93-148.

IARC (1985), Tobacco Habits Other Than Smoking: Betel-Quid and Areca-Nut Chewing and Some Related Nitrosamines. IARC, Lyon, France, **IARC Monograph 37.**

IARC (1986), Chemistry and Analysis of Tobacco Smoke. In *Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Smoking.* IARC, Lyon, France, **IARC Monograph 38:** 83-126, 387-394.

Ingebrethsen BJ (1986a), Aerosol Studies of Cigarette Smoke. RECENT ADV. TOB. SCI. *12:* 54-142.

Ingebrethsen BJ (1986b), Evolution of the Particle Size Distribution of Mainstream Cigarette Smoke during a Puff. AEROSOL SCI. TECH. *5:* 423-433.

Ingebrethsen BJ (1989), The Physical Properties of Mainstream Cigarette Smoke and Their Relation to Deposition in the Respiratory Tract. In Crapo JD, Smolko ED, Miller FJ, Graham JA, and Hayes AW (Editors), *Extrapolation of Dosimetric Relationships for Inhaled Particles and Gases*, Academic Press, New York NY: 125-142.

Ingebrethsen BJ, Heavner DL, Angel AL, Conner JM, Steichen TJ, and Green CR (1988), A Comparative Study of Environmental Tobacco

Smoke Particulate Matter Measurements in an Environmental Chamber. J. AIR POLLUT. CONT. ASSOC. *38:* 413-417.

Ingebrethsen BJ and Sears SB (1989), Particle Evaporation of Sidestream Cigarette Smoke in a Stirred Tank. J. COLLOID INTERFACE SCI. *131:* 526-536.

Ingebrethsen BJ, Sears SB, and Boldridge DW (1990), Evaporation and Growth of Smoke Particles from Two Types of Cigarettes. 44th TOB. CHEM. RES. CONF., Winston-Salem NC: Paper No. 23.

Iyengar JR, Panalaks T, Miles WF, and Sen NP (1976), J. SCI. FOOD *27:* 527-530.

Janzowski C, Eisenbrand G, and Preussmann R (1978a), J. CHROMATOG. *150:* 216-220.

Janzowski C, Eisenbrand G, and Preussmann R (1978b), FOOD COSMET. TOXICOL. *16:* 343-348.

Jarvis M, Tunstall-Pedoe H, Feyerband C, Vesey C, and Salloojee Y (1984), Biochemical Markers of Smoke Absorption and Self-Reported Exposure to Passive Smoking. J. EPIDEMIOL. COMMUNITY HLTH. *38:* 335-339.

Jasinski JS (1984), Liquid Chromatographic Determination of Nitrosamines in Malt and Beer with a Photoconductivity Detector. ANAL. CHEM. *56:* 2214-2218.

Jinot J and Bayard S (1994), Respiratory Health Effects of Passive Smoking: EPA's Weight-of-Evidence Analysis. J. CLIN. EPIDEMIOL. *47:* 339-349.

Josefsson E and Nygren S (1981), VAR FÔDA *33 (Suppl. 2):* 147-165.

Kaburaki Y, Sugawara S, Kobashi U, and Doihara T (1970), Studies on the Composition of Tobacco Smoke. XIV. The Formation of Pyridines in the Pyrolysis of Nicotine. J. AGR. CHEM. SOC. JAPAN *44:* 224-231.

Kado NY, Manson C, Eisenstadt E, and Hsieh DPH (1985), The Kinetics of Mutagen Excretion in the Urine of Cigarette Smokers. MUTATION RES. *157:* 227-232.

Kakhiani ZN (1955), Cancerogenic Action of Tobacco Tar. VOPROSY ONKOL. *1:* 96-100.

Kallistratos G (1975), Verhinderung der 3,4-Benzopyren-kanzerogenese durch natürliche und synthetische Verbindungen. MUNCH. MED. WCHNSCHR *117:* 391-394 .

Kallistratos G and Fasske E (1976), Biologische Inactivierung kanzerogener Stoffe. FOLIA BIOCH. BIOL. GRAECA *13:* 94-107.

Kamata K, Motohashi N, Meyer R, and Yamamoto Y (1992), J. LIQ. CHROMATOG. *15:* 1907.

Kann J, Tauts O, Kalve R, and Bogovski P (1982), In IARC, N-*Nitroso Compounds: Occurrence and Biological Effects*, IARC, Lyon, France, IARC SCI. PUBL. NO. 41: 319-326.

Kawabata T, Ohshima H, Uibu J, Nakamura M, Matsui M, and Hamano M (1979), In *Naturally Occurring Carcinogens/Mutagens and Modulators of Carcinogenesis*, University Park MD: 195-209.

Kawabata T, Uibu J, Ohshima H, Matsui M, Hamano M, and Tokiwa H (1982), In IARC, N-*Nitroso Compounds: Occurrence and Biological Effects*, IARC, Lyon, France, IARC SCI. PUBL. NO. 41: 481-490.

Kennaway EL (1948), Some Notes on Cancer Research. ACTA UNIO INTERNAT CONTRA CANCRUM *6:* 934.

Kennaway EL and Hieger I (1930), BRIT. MED. J. *1930(i):* 1044.

Kennaway EL and Lindsey AJ (1958), Some Possible Exogenous Factors in the Causation of Lung Cancer. BRIT. MED. BULL. *14:* 124-131.

Ketkar MB, Holste J, Preussmann R, and Althoff J (1983), Carcinogenic Effect of Nitrosomorpholine Administered in the Drinking Water to Syrian Golden Hamsters. CANCER LETT. *17:* 333-338.

Ketkar MB, Schneider P, Preussmann R, Plass C, and Mohr U (1982), Carcinogenic Effect of Low Doses of Nitrosopyrrolidine Administered in Drinking Water in Syrian Golden Hamsters. J. CANCER RES. CLIN. ONCOL. *104:* 775-79.

Kimoto WI, Dooley CJ, Carre J, and Fiddler W (1980), WATER RES. *14:* 869-876.

Klein D, Girad AM, DeSmedt J, Fellion Y, and Derby G (1981), FOOD COSMET. TOXICOL. *19:* 233-235.

Klein M (1965), Inhibition of Skin Tumorigenesis in Strain b6afl/j Female Mice with Maleic Anhydride. J. NATL. CANCER INST. *34:* 175-183.

Klus H (1990), Distribution of Mainstream and Sidestream Cigarette Smoke Components. RECENT ADV. TOB. SCI. *16:* 189-232.

Klus H, Begutter H, Ball M, and Intorp M (1987), Environmental Tobacco Smoke in Real Life Situations. In Seifert B, Esdorn H, Fisher M, Rüden H, and Wegner J (Editors), *Indoor Air '87, Vol. 2: Environmental Tobacco Smoke, Multicomponent Studies, Radon, Sick Buildings, Odours and Irritants, Hyperreactivities and Allergies,* Institute for Water, Soil and Air Hygiene, Berlin, Germany: 137-141.

Klus H and Kuhn H (1982), Verteilung verschiedener Tabakrauchbestandteile auf Haupt- und Nebenstromrauch (Eine Übersicht). BEITR. TABAKFORSCH. INTERNAT. *11:* 229-265.

Komczynski L (1958), Morphological Changes in the Organs of Mice under the Influence of Tobacco Smoke. NAKLADEM. MARCHLEWSKIEGO BIAL. SUPPL. *2:* 1-62.

Kosak AI (1954), The Composition of Tobacco Smoke. EXPERIENTIA *10:* 69-71.

Kotin P and Falk HL (1963), ADV. CANCER RES. *7:* 475-514.

Kovacs K and Somogyi A (1970), Suppression by Spironolactone of 7,12-Dimethylbenz[*a*]anthracene-Induced Mammary Tumors. EUROP. J. CANCER *6:* 195-201.

Krahnert R (1953), Lung Cancer in Dogs. VET. PATHOL. INST., LEIPZIG

Kröller E (1964), Ergebnisse vergleichender Schwel- und Rauchversuche an Tabak. DEUT. LEBENSM. RUNDSCHAU *60:* 214-215.

Kröller E (1967), Untersuchungen zum Nachweiss von Nitrosaminen in Tabakrauch und Lebensmitteln. DEUT. LEBENSM. RUNDSCHAU *63:* 303-305.

Krull IS, Fan TY, and Fine DH (1978), Problem of Artifacts in the Analysis of *N*-Nitroso Compounds. ANAL. CHEM. *50:* 698-701.

Kuenzi W, Chau J, Norkus E, Holowaschenko H, Newmark H, Mergens W, and Conney AN (1984), Caffeic and Ferulic Acid as Blockers of Nitrosamine Formation. CARCINOGENESIS *5:* 309-314.

Kumar R, Siddiqi M, Tricker AR, and Preussmann R (1991), Tobacco-Specific *N*-Nitrosamines in Tobacco and Mainstream Smoke of Indian Cigarettes. FOOD. CHEM. TOXICOL. *29:* 405-408.

Lacassagne A, Buu-Hoï NP, Daudel R, and Zajdela F (1956), The Relation between Carcinogenic Activity and the Physical and Chemical Properties of Angular Benzacridines. ADV. CANCER RES. 4, 316-369.

Lacassagne A, Buu-Hoï NP, and Rudall G (1945), Inhibition of the Carcinogenic Action Produced by a Weakly Carcinogenic Hydrocarbon on a Highly Active Hydrocarbon. BRIT. J. EXPTL. PATH. *26:* 5-12.

Lakritz L and Pensabene JW (1981), J. DAIRY SCI. *64:* 371-374.

Lam J (1955), 3,4-Benzopyrene as a Product of the Pyrolysis of Aliphatic Hydrocarbons. ACTA PATH. MICROBIOL. SCAND. *37:* 421-428.

Lam J (1956), Determination of 3,4-Benzopyrene and Other Aromatic Hydrocarbons Formed by Pyrolysis of Aliphatic Tobacco Hydrocarbons. ACTA PATH. MICROBIOL. SCAND. *39:* 207-210.

Laskowski K (1951), Components of Tobacco Smoke and Their Absorption in the Respiratory System of the Smoker. ROCZ. PANSTWOWEGO ZADLAKU HIG. *2:* 139-160.

Laurene AH, Young GW, and Lyerly LA (1963), Factors Which Affect the Phenol Content of Cigarette Smoke. Personal communication.

Lavit-Lamy D and Buu-Hoï NP (1966), The True Nature of "Dibenzo[*a,l*]pyrene" and Its Known Derivatives. CHEM. COMM. *4:* 92-94.

Lazar PH, Chouroulinkov I, Libermann C, and Guerin M (1966a), Amounts of 3,4-Benzpyrene (3,4-BP) in Cigarette Smoke Condensates and Carcinogenicity. 9TH INTERNAT. CANCER CONG., Tokyo, Japan.

Lazar PH, Chouroulinkov I, Libermann C, and Guerin M (1966b), Benzo[*a*]pyrene Content and Carcinogenicity of Cigarette Smoke Condensate: Results of Short-Term and Long-Term Tests. J. NATL. CANCER INST. *37:* 573-579.

LeBouffant L, Martin JC, Daniel H, Henin JP, and Normand C (1980), Action of Intensive Cigarette Smoke Inhalations on the Rat Lung. Role of Particulate and Cofactors. J. NATL. CANCER INST. *64:* 273-284.

Lee CK, Brown BG, Reed EA, *et al.* (1992), Fourteen-Day Inhalation Study in Rats, Using Aged and Diluted Sidestream Smoke from a Reference Cigarette. FUND. APPL. TOXICOL. *19:* 141-146.

Lee CK, Brown BG, Reed EA, *et al.* (1993), Ninety-Day Inhalation Study in Rats, Using Aged and Diluted Sidestream Smoke from a Reference Cigarette: DNA Adducts and Alveolar Macrophage Cytogenetics. FUND. APPL. TOXICOL. *20:* 393-401.

Lee CK, Doolittle DJ, Burger GT, and Hayes AW (1990), Comparative Genotoxicity Testing of Mainstream Whole Smoke from Cigarettes Which Burn or Heat Tobacco. MUTATION RES. *242:* 37-45.

Lee CK and Fulp C (1991), Personal communication.

Lee CK, Fulp C, and Chang KM (1991), Personal communication.

Lee CK, Munoz JA, Fulp C, Chang KM, Rogers J, Borgerding MF, and Doolittle DJ (1993), Inhibitory Activity of Cigarette Smoke Condensate on the Mutagenicity of Heterocyclic Amines. MUTATION RES. In print.

Lee CK and Reed EA (1983), Effect of Nicotine on the Mutagenicity of *N*-Nitrosodimethylamine and Benzo[*a*]pyrene. Personal communication.

Leuchtenberger C and Leuchtenberger R (1962), A Correlated Histological, Cytological, and Cytochemical Study of the Major Bronchi from Mice Exposed to Cigarette Smoke. In James G and Rosenthal T (Editors), *Tobacco and Health,* Charles C. Thomas, Springfield IL: 87-104.

Leuchtenberger C and Leuchtenberger R (19??), Effects of Chronic Inhalation of Whole Fresh Cigarette Smoke and of Its Gas Phase on Pulmonary Tumorigenesis in Snell's Mice. [Incomplete reference cited by OSHA (No. 8-197)].

Leuchtenberger C, Leuchtenberger R, and Doolin PF (1958), A Correlated Histological, Cytological, and Cytochemical Study of the Tracheobronchial Tree and Lungs of Mice Exposed to Cigarette Smoke. I. Bronchitis with Atypical Epithelial Changes in Mice Exposed to Cigarette Smoke. CANCER *11:* 490-506.

Leuchtenberger C, Leuchtenberger R, Zebrun W, and Shaffer P (1960a), A Correlated Histological, Cytological, and Cytochemical Study of the Tracheobronchial Tree and Lungs of Mice Exposed to Cigarette Smoke. II. Varying Response of Major Bronchi to Cigarette Smoke. Absence of Bronchogenic Cancer after Prolonged Exposure and Disappearance of Bronchial Lesions after Cessation of Exposure. CANCER *13:* 721-732.

Leuchtenberger C, Leuchtenberger R, Zebrun W, and Shaffer P (1960b), A Correlated Histological, Cytological, and Cytochemical Study of the Tracheobronchial Tree and Lungs of Mice Exposed to Cigarette Smoke. III. Unaltered Incidence of Grossly Visible Adenomatous Lung Tumors in Female CF1 Mice After Prolonged Exposure to Cigarette Smoke. CANCER *13:* 956-958.

Libbey LM, Scanlan RA, and Barbour JF (1980), FOOD COSMET. TOXICOL. *18:* 459-461.

Lijinsky W (1990), Occupational and Environmental Exposures to *N*-Nitroso Compounds. ADV. MOD. ENVIRON. TOXICOL. *17:* 189-207.

Lijinsky W and Shubik P (1964), Benzo[*a*]pyrene and Other Polynuclear Hydrocarbons in Charcoal-Broiled Meat. SCIENCE *145:* 53.

Lijinsky W and Shubik P (1965), Polynuclear Hydrocarbon Carcinogens in Cooked Meat and Smoked Food. IND. MED. SURG. *34:* 152.

Liu L and Castonguay A (1991), Inhibition of the Metabolism and Genotoxicity of 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in Rat Hepatocytes by (+)-Catechin. CARCINOGENESIS *12:* 1203-1208.

Lo LW and Stich HF (1978), The Use of Short-Term Tests to Measure the Preventive Action of Reducing Agents on Formation and Activation of Carcinogenic Nitroso Compounds. MUTATION RES. *57:* 57-67.

Lombard LS and Witte EJ (1959), Frequency and Types of Tumors in Mammals and Birds of the Philadelphia Zoological Garden. CANCER RES. *19:* 127-141.

Lorenz E, Stewart HL. Daniel JH, and Nelson CL (1943), The Effects of Breathing Tobacco Smoke on A Strain Mice. CANCER RES. *3:* 123-124.

Lupu NG and Veliçan C (1957), Pulmonary Sclerosis due to Tabagism. PRESSE MED. *65:* 2184-2187.

Lyons MJ (1958), Presence of 1,2,3,4-Dibenzpyrene in Cigarette Smoke. NATURE *182:* 178.

Lyons MJ (1962), Comparison of Aromatic Polycyclic Hydrocarbons from Gasoline Engine and Diesel Engine Exhausts, General Atmospheric Dust, and Cigarette Smoke Condensate. In Sawicki E and Cassel K (Editors), *Symposium: Analysis of Carcinogenic Air Pollutants*, NATL. CANCER INST. MONOGRAPH 9: 193-199.

Lyons MJ and Johnston H (1957), Chemical Analysis of the Neutral Fraction of Cigarettes Smoke Tar, BRIT. J. CANCER *11:* 554-562.

Maduagwu EN and Bassir O (1979), TOXICOL. LETT. *4:* 169-173.

Maga JA (1988), Potential Health Concerns Associated with Smoke. Chapter 10 in Maga JA, *Smoke in Food Processing*, CRC Press Inc., Boca Raton FL: 113-144.

Magee PN (1984), Summary and Closing Remarks. In O'Neill IK, von Borstel RC, Miller CT, Long J, and Bartsch H (Editors), N-*Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer*, IARC, Lyon, France, IARC SCI. PUBL. NO. 57: 985-988,

Magee PN and Barnes JM (1956), The Production of Malignant Hepatic Tumours in the Rat by Feeding with Dimethylnitrosamine. BRIT. J. CANCER *10:* 114-122.

Magee PN and Barnes JM (1967), Carcinogenic Nitroso Compounds. ADV. CANCER RES. *10:* 163-246.

Magee PN, Montesano R, and Preussmann R (1976), *N*-Nitroso Compounds and Related Carcinogens. In Searle CE (Editor), *Chemical Carcinogens*. AM. CHEM. SOC. MONOGRAPH 173: 491-525.

Maki T, Tamura Y, Shimamura Y, Koseki M, Nishigaki S, and Naoi Y (1979), TOKYO-TORITSU EISEI KENYUSHO KENKYO *30:* 145-148.

Maki T, Tamura Y, Shimamura Y, Koseki H, Nishigaki S, and Naoi Y (1980a), SHOKUKUHIU EISEIGAKU ZASSHI *21:* 184-188.

Maki T, Tamura Y, Shimamura Y, and Naoi Y (1980b), Estimated Volatile Nitrosamines in Japanese Food. BULL. ENVIRON. CONTAM. TOXICOL. *25:* 257-261.

Mandagere A (1986), Smoke-Related *N*-Nitroso Compounds in Cured Meat Systems. DISSERTATION.

Mangino MM, Scanlan RA, and O'Brien T (1982), In Scanlan RA and Tannenbaum SR (Editors), N-*Nitroso Compounds*, Am. Chem. Soc. Symp. Series No. 174, American Chemical Society, Washington DC: 229-245.

Masami T, Ohshima H, and Kawabata T (1980), NIPPON SUISAN GAKKAISHI *46:* 587-590.

Massey RC, Key PE, Jones RA, and Logan GL (1991), Volatile, Nonvolatile and Total *N*-Nitroso Compounds in Bacon. FOOD ADD. CONTAM. *8:* 585-598.

Matsui M and Kaya K (1992), *N*-Nitroso Compounds in the Environment. KANKYO KAGAKU *2:* 1-17.

Matsukura S, Taminato T, Kitano N, Seino Y, Hamada H, Uchihashi M, Nakijima H, and Hirata Y (1984), Effects of Environmental Tobacco Smoke on Urinary Cotinine Excretion in Nonsmokers. NEW ENG. J. MED. *311:* 828-832.

Matsumoto M, Oyasu R, Hopp ML, and Kitajima T (1977), Suppression of Dibutylnitrosamine-Induced Bladder Carcinomas in Hamsters by Dietary Indole. J. NATL. CANCER INST. *58:* 1825-1828.

Matsushita H and Mori T (1984), Nitrogen Dioxide and Nitrosamine Levels in Indoor Air and Sidestream Smoke of Cigarettes. In Berglund B, Lindvall T, and Sundell J (Editors), *Indoor Air, Vol. 2: Radon, Passive Smoking, Particulates and Housing Epidemiology*, Swedish Council for Building Research, Stockholm, Sweden: 335-340.

Mauderly GL. Jones RK, Griffith WC, Henderson RF, and McClellan RO (1987), Diesel Exhaust Is a Pulmonary Carcinogen in Rats Exposed Chronically by Inhalation. FUND. APPL. TOXICOL. *9:* 208-221.

McAughey JJ, Knight DA, Black A, and Dickens CJ (1994), Estimation of Environmental Tobacco Smoke (ETS) Retention in Human Volunteers from Measurements of Exhaled Smoke Composition. INHAL. TOXICOL. In press.

Mejstrik V, Drzkova L, Sagner Z, Matrka M, and Krampera F (1987), Occurrence and Properties of *N*-Nitroso Compounds. CHEM. LISTY *81:* 357-362.

Menzie CA, Potocki BB, and Santodonato J (1992), Exposure to Carcinogenic PAHs in the Environment. ENVIRON. SCI. TECHNOL. *26:* 1278-1284.

Mergens WJ, Kamm JJ, Newmark HL, Fiddler W, and Pensabene J (1978), α-Tocopherol: Uses in Preventing Nitrosamine Formation. In Walker EA, Griciute L, Castegnaro M, and Lyle RE (Editors), *Environmental Aspects of* N-*Nitroso Compounds*, IARC, Lyon, France, IARC SCI. PUBL. NO. 19: 199-212.

Mertens VE (1941), Noch einmal Zigarettenrauch und Lungenkrebs. Z. KREBSFORSCH. *51:* 183-192.

Microbiological Associates (1984), Corollary Studies: Pharmokinetics of Inhaled Materials. Chapter VI in Henry CJ and Kouri RE (Project Directors), *Chronic Exposure of Mice to Cigarette Smoke.* Field, Rich & Associates, New York NY: 166-178.

Miller JA and Miller EC (1953), The Carcinogenic Aminazo Dyes. ADV. CANCER RES. *1:* 339-396.

Mirvish SS (1981a), Ascorbic Acid Inhibition of *N*-Nitroso Compound Formation in Chemical, Food and Biological Systems. In Zedeck MS and Lipkin M (Editors), *Inhibition of Tumor Induction and Development*, Plenum Publishing Corp., New York: 101-126.

Mirvish SS (1981b), Inhibition of the Formation of Carcinogenic *N*-Nitroso Compounds by Ascorbic Acid and Other Compounds. In Burchenal JH and Oettgen HF (Editors), *Cancer Achievements, Challenges and Prospects for the 1980's*, Plenum Publishing Corp., New York NY: 557-588.

Mirvish SS (Oct. 15 Suppl., .986), Effect of Vitamin C and E on *N*-Nitroso Compound Formation, Carcinogenesis and Cancer. CANCER *58:* 1842-1850.

Mirvish SS, Cardesa A, Wallcave L, and Shubik P (1975), Induction of Lung Adenomas by Amines or Ureas Plus Nitrite and by *N*-Nitroso Compounds: Effects of Ascorbate, Gallic Acid, Thiocyanate, and Caffeine. J. NATL. CANCER INST. *55:* 633-636.

Mirvish SS and Shubik P (1974), Ascorbic Acid and Nitrosamine. NATURE *250:* 684.

Mirvish SS, Wallcave L, Eagen M, and Shubik P (1972), Ascorbate-Nitrate Reaction: Possible Means of Blocking the Formation of Carcinogenic *N*-Nitroso Compounds. SCIENCE *177:* 65-68.

Mizusaki S, Takashima T, and Tomaru K (1977b), Factors Affecting Mutagenic Activity of Cigarette Smoke Condensate in *Salmonella typhimurium* TA1538. MUTATION RES. *48:* 29-36.

Mohr U and Reznik G (1978), Tobacco Carcinogenesis. In Harris CC (Editor), *Pathogenesis and Therapy of Lung Cancer*, Marcel Dekker, New York NY: 263-267.

Mohtashamipur E, Mohtashamipur A, Germann PG, Ernst H, Norpoth K, and Mohr U (1990), Comparative Carcinogenicity of Cigarette Mainstream and Sidestream Smoke Condensates on the Mouse Skin. J. CANCER RES. CLIN. ONCOL. *116:* 604-608.

Mohtashamipur E, Muller G, Norpoth K, Endrikat M, and Stucker W (1987), Urinary Excretion of Mutagens in Passive Smokers. TOXICOL. LETT. *35:* 141-146.

Morie GP and Sloan CH (1973), Determination of *N*-Nitrosodimethylamine in the Smoke of High Nitrate Tobacco Cigarettes. BEITR. TABAKFORSCH. *7:* 61-66.

Motohashi N, Kamata K, and Meyer R (1993), Chromatographic Techmiques Used to Determine Benz[*c*]acridines in Environmental Samples. J. CHROMATOG. *643:* 1-10.

Motulionis DH (1984), Chronic Cigarette Smoke Inhalation and Aging Mice. Morphological and Functional Lung Abnormalities. EXP. LUNG RES. *7:* 237-256.

Mühlbock O (1955), The Carcinogenic Action of Cigarette Smoke in Mice. MED. TIJDSCHR. GENEESK. *99:* 2276-2278.

Mumford JL, Harris DB, and Williams K (1987), Indoor Air Sampling and Mutagenicity Studies from Unvented Coal Combustion. ENVIRON. SCI. TECH. *21:* 308-311.

Murphy SE and Heilbrun R (1990), Effect of Nicotine and Tobacco-Specific Nitrosamines on the Metabolism of *N'*-Nitrosonornicotine and 4-

(Methylnitrosamino)-1-(3-pyridyl)-1-butanone by Rat Oral Tissue. CARCINOGENESIS *11:* 1663-1666.

National Academy of Science (1986), *Environmental Tobacco Smoke: Measuring Exposure and Assessing Health Effects*. National Research Council, National Academy of Science Press, Washington DC.

National Cancer Institute (1980), *Report No. 5. Toward Less Hazardous Cigarettes. Summary: Four Skin Painting Bioassays Using Condensate from Experimental Cigarettes.* DHEW Publ. (NIH) (September 1980).

Neal J and Rigdon RH (1967), TEXAS RPT. BIOL. MED. *25:* 553.

Nelson PR, Heavner DL, and Collie BB (1989), Characterization of Environmental Tobacco Smoke Generated by Different Cigarettes. In Bieva CJ, Courtois Y, and Govaerts M (Editors), *Present and Future of Indoor Air Quality,* Elsevier Science Publishers, Biomedical Division: 277-282.

Nesemann E, Schröder R, and Seehofer F (1968), Methoden zur quantitativen Bestimmung von Insektiziden in Tabak und Tabakrauch. I. Mitteilung: Zur Bestimmung von Organo-Chlor-Insektiziden. BEITR. TABAKFORSCH. *4:* 182-188.

Neurath G, Pirmann B, Lüttich W, and Wichern H (1965), Zum Frage der *N*-Nitroso-Verbindungen im Tabakrauch. II. BEITR. TABAKFORSCH. *3:* 251-262.

Neurath G, Pirmann B, and Wichern H (1964), Zum Frage der *N*-Nitroso-Verbindungen im Tabakrauch. BEITR. TABAKFORSCH. *2:* 311-319.

Newmark H and Mergens W (1981), α-Tocopherol (Vitamin E) and Its Relationship to Tumor Induction. In Zedeck MS and Lipken M (Editors), *Inhibition of Tumor Induction and Development*, Plenum Publishing, New York NY: 127-168.

Nielsen SW (1965), Spontaneous Pulmonary Tumors of the Dog. INTERNAT CONF. ON LUNG TUMORS IN ANIMALS, Perugia, Italy (June 24-29).

Nieper L and Etzel V (1983), Nitrate Content in Smoked Fish Muscle. LEBENSMITTELHYG. *34:* 149.

Nitrite Safety Council (1980), FOOD TECHNOL. *34:* 45-51, 53, 103. (m127)

Nomura T (1980), Timing of Chemically Induced Neoplasia in Mice Revealed by the Antineoplastic Action of Caffeine. CANCER RES. *40:* 1332-1340.

Nomura T (1983), Comparative Inhibiting Effect of Methylxanthines on Urethan-Induced Tumors, Malformations and Presumed Somatic Mutations in Mice. CANCER RES. *43:* 1342-1346.

Occupational Safety and Health Administration (OSHA) (1994), Indoor Air Quality. FED. REG. *59 (No. 65):* 15968-16039.

Okieimen F, Akintola E, Anucha T, and Ajibola M (1985), Determination of the Total Level of Nitrosamine Contamination of Some Consumer Products in Nigeria. INTL. J. ENV. ANAL. CHEM. *21:* 261-266.

Orris L, Van Duuren BL, Kosak AI, Nelson N, and Schmitt FL (1958), The Carcinogenicity for Mouse Skin and the Aromatic Hydrocarbon Content of Cigarette-Smoke Condensate. J. NATL. CANCER INST. *21:* 557-561.

Otto H and Elmenhorst H (19??), Experimentelle Untersuchungen zur Tumorinduktion mit der Gasphase. [Incomplete reference cited by OSHA (1994)].

Panalaks T, Iyengar JR, and Sen NP (1973), Nitrate, Nitrite and *N*-Nitrosodimethylamine in Cured Meat Products. J. ASSOC. OFF. ANAL. CHEM. *56:* 621-625.

Panalaks T, Iyengar JR, Donaldson BA, Miles WF, and Sen NP (1974), Further Survey of Cured Meat Products for Volatile *N*-Nitrosamines. J. ASSOC. OFF. ANAL. CHEM. *57:* 806-812.

Passey RD (1957), Carcinogenicity of Cigarette Tars. BRIT. EMP. CANCER CAMP., ANN. RPT. *35:* 65-66.

Passey RD (1958), Cigarette Smoking and Cancer of the Lung. BRIT. EMP. CANCER CAMP., ANN. RPT. *36:* 48-49.

Passey RD, Roe EMF, Middleton FZ, Bergel F, Everett JL. Lewis GE, Martin JB, Boyland E, and Sims P (1954), Cigarette Smoking and Cancer. BRIT. EMP. CANCER CAMP., ANN. RPT. *32:* 60-62.

Patrianakos CP and Hoffmann D (1979), Chemical Studies on Tobacco Smoke. LXIV. On the Analysis of Aromatic Amines in Cigarette Smoke. J. ANAL. TOXICOL. *3:* 150-154.

Peacock PR (1958), Cigarette Smoking by Laboratory Animals. 7th INTERNAT. CANCER CONGR., London UK (July 6-12).

Pedersen E and Meyland I (1981), Nitrate, Nitrite, and Volatile Nitrosamines in Pickled Fish Prepared by Addition of Nitrate. Z. LEBENSM. UNTERFORSCH. *173:* 359-361.

Pensabene JW, Feinberg JI, Piotrowski EG, and Fiddler W (1979), Occurrence and Determination of *N*-Nitrosoproline and *N*-Nitrosopyrrolidine in Cured Meat Products. J. FOOD SCI. *44:* 1700-1702.

Pensabene JW, Miller AJ, Greenfield EL, and Fiddler W (1982), Rapid Dry Column Method for Determination of *N*-Nitrosopyrrolidine in Fried Bacon. J. ASSOC. OFF. ANAL. CHEM. *65:* 151-156.

Perchellet JP and Boutwell RK (1981), Effects of 3-Isobutyl-1-methylxanthine and Cyclic Nucleotides on the Chemical Processes Linked to Skin Tumor Promotion by 12-*O*-Tetradecanoylphorbol-13-acetate. CANCER RES. *41:* 3927-3935.

Perera F (1981) Carcinogenicity Of Particulate Benzo(*a*)pyrene: An Appraisal of the Evidence and the Need for Control. ENVIRON. HLTH. PERSPECTIVES *42:* 163-185.

Peto R and Doll R (1985), The Control of Lung Cancer. NEW SCIENTIST *105 (1440):* 26–30.

Pietzsch A (1959), Zum Nachweis cancerogenen Kohlenwasserstoffen im Tabakrauch. PHARMAZIE (Berlin) *14:* 466-473.

Poel WE (1956), Carcinogens and Minimal Carcinogenic Doses. SCIENCE *123:* 588.

Pollock JRA (1981), J. INST. BREWING *87:* 356-359.

Preussmann R (1983b), Public Health Significance of Environmental *N*-Nitroso Compounds. In Egan H, Preussmann R, Eisenbrand G, Spiegelhalder B, O'Neill IK, and Bartsch H, Environmental Carcinogens: Selected Methods of Analysis. Vol. 6: N-*Nitroso Compounds*, IARC, Lyon, France. IARC SCI. PUBL. NO. 45: 3-17.

Preussmann R and Eisenbrand G (1984), *N*-Nitroso Carcinogens in the Environment. Chapter 13 in Searle CE (Editor), *Chemical Carcinogens. Second Edition*, American Chemical Society Monograph 182, American Chemical Society, Washington DC: 829-868.

Preussmann R, Neurath G, Wulf-Lorentzen G, Daiber D, and Hengy H (1964), Anfärbemethoden und Dünnshicht-Chromatographie von organischen *N*-Nitrosoverbindungen. Z. ANAL. CHEM. *202:* 187-192.

Preussmann R, Spiegelhalder B, and Eisenbrand G (1980), In *Carcinogenesis: Fundamental Mechanisms and Environmental Effects*, Reidel Publishing Co., The Netherlands: 273-285.

Preussmann R, Spiegelhalder B, and Eisenbrand G (1982b), Reduction of Human Exposure to Environmental *N*-Nitroso Compounds. In Scanlan RA and Tannenbaum SR (Editors), N-*Nitroso Compounds*, Am. Chem. Soc. Symp. Series No. 174, American Chemical Society, Washington DC: 217-228.

Preussmann R and Stewart BW (1984), *N*-Nitroso Carcinogens. Chapter 12 in Searle CE (Editor), *Chemical Carcinogens. Second Edition*, American Chemical Society Monograph 182, American Chemical Society, Washington DC: 643-828.

Putzrath RM, Langley D, and Eisenstadt E (1981), Analysis of Mutagenic Activity in Cigarette Smoker' Urine by High Performance Liquid Chromatography. MUTATION RES. *85:* 97-108.

Pyriki C (1962), Polycyclische und aliphatische Kohlenwasserstoffe des Tabakrauches. GERMAN CHEM. SOC., ANN. MTG., Leipzig DDR.

Pyriki C (1963), Polycyclische und aliphatische Kohlenwasserstoffe des Tabakrauches. DIE NAHRUNG *7:* 439-448.

Ramel C, Alekperov UK, Ames BN, Kada T, and Wattenberg LW (1986), Inhibitors of Mutagenesis and Their Relevance to Carcinogenesis. Report by ICPEMC Expert Group on Antimutagens and Desmutagens. MUTATION RES. *168:* 47-65.

Rathkamp G, Chao DK, and Hoffmann D (1973), Analytical Studies on Nonvolatile *N*-Nitrosamines in Cigarette Smoke. 27th TOB. CHEM. RES. CONF., Winston-Salem NC: Paper No. 26.

Reasor MJ (1987), The Composition and Dynamics of Environmental Tobacco Smoke. J. ENVIRON. HLTH. *50:* 20-24.

Reasor MJ (1990), Biological Markers in Assessing Exposure to Environmental Tobacco Smoke. Chapter 4 in Ecobichon DJ and Wu JM (Editors), *Environmental Tobacco Smoke*, PROC. INTERNAT. SYMP., McGill University 1989, Lexington Books, DC Heath and Company, Lexington MA: 69-77.

Registry of Toxic Effects of Chemical Substances (1987), *1985-1986 Edition User's Guide*. DHHS Publ. No. (PHS) 87-114.

Reif JS, Dunn K, Ogilvie GK, and Harris CK (1992), Passive Smoking and Canine Lung Cancer Risk. AM. J. EPIDEMIOL. *135:* 234-239.

R. J. Reynolds Tobacco Company (1988), *Chemical and Biological Studies on New Cigarette Prototypes That Heat Instead of Burn Tobacco*. R. J. Reynolds Tobacco Company, Winston-Salem NC.

Roberts DL and Rowland RL (1962), Macrocyclic Diterpenes. α- and β-4,8,13-Duvatriene-1,3-diols from Tobacco. J. ORG. CHEM. *27:* 3989-3995.

Rodgman A (1960), Personal communication with R.J. Reynolds Tobacco Company R&D management re U.S. patent issued to Commercial Solvents on the industrial preparation of *N*-nitrosodialkylamines by the reaction of dialkylamines with methyl nitrite, *cf.* Tindall JB (1960), Lower Nitrosodialkylamines. U.S. Patent No. 2,947,785 (August 2).

Rodgman A (1991), A Comparison of the Chemical and Physical Properties of Cigarette Mainstream Smoke (MS), Cigarette Sidestream Smoke (SS), and Environmental Tobacco Smoke (ETS). Document submitted to the Environmental Protection Agency, December, 1991. Revised version submitted June, 1992.

Rodgman A (1992), Environmental Tobacco Smoke. REGUL. TOXICOL. PHARMACOL. *16:* 223-244.

Rodgman A (1993), The Composition of Cigarette Smoke. The Polycyclic Aromatic Hydrocarbons. A Retrospective. Submitted to BEITR. TABAKFORSCH. INTERNAT. (23 April).

Rodgman A and Cook LC (1960), The Composition of Cigarette Smoke. IV. α-Tocopherol. TOB. SCI. *4:* 7-8.

Rodgman A and Cook LC (1962), The Composition of Cigarette Smoke. XI. Heterocyclic Nitrogen Compounds from Turkish Tobacco Smoke. TOB. SCI. *6:* 176-179.

Rodgman A and Cook LC (1965), The Composition of Cigarette Smoke. Presented in part at Sigma Xi Meeting, Wake Forest University, Winston-Salem NC (17 March, 1965), American Chemical Society Meeting, Columbus GA (2 May, 1968), and Central North Carolina Section Meeting, American Chemical Society, Greensboro NC (14 October, 1969).

Rodgman A, Mims SS, and Cook LC (1964), Unpublished data on mouth absorption of vapor-phase components of mainstream smoke.

Roe FJC (1962), The Role of 3,4-Benzopyrene in Carcinogenesis by Tobacco Smoke Condensate. NATURE *194:* 1089-1090.

Roe FJC (1963), Role of 3,4-Benzpyrene in Carcinogenesis by Tobacco Smoke Condensate. ACTA UNIO INTERNAT. CONTRA CANC. *19:* 730.

Roffo AH (1942), El Alquitran de Tabaco Extraido y la Disminucion de Cancerizacion. BOL. INST. MED. EXPTL. ESTUD. CANCER *19:* 431-502.

Rõper H (1983), Chemie und Bilding von *N*-Nitrosoverbindungen. In Preussmann R (Editor), *Das Nitrosamin-Problem*. Verlag Chemie, Weinheim: 189-211.

Rõper H, Heyns K, and Guenther W (1981), MIKROBIOL. TECHNOL. LEBENSMITT. *7:* 13-17.

Rosenblatt DH, Dacre JC, and Cogley DR (1982), An Environmental Fate Model Leading to Preliminary Pollutant Limit Values for Human Health Effects. In Conway RA (Editor), *Environmental Risk Analysis for Chemicals*, Van Nostrand Reinhold, New York NY : 475-505.

Rosin MP (1982), Inhibition of Genotoxic Activities of Complex Mixtures by Naturally Occurring Agents. CARC. MUTAGEN IN ENVIRON. *1:* 259-273.

Ross RD, Morrison J, Rounbehler DP, Fan S, and Fine DH (1977), J. AGR. FOOD CHEM. *25:* 1416-1418.

Rowland RL (1958), Flue-Cured Tobacco. III. Solanachromene and α-Tocopherol. J. AM. CHEM. SOC. *80:* 6130-6133.

Rowland RL, Rodgman A, Schumacher JN, Roberts DL, Cook LC, and Walker WE Jr (1964), Macrocyclic Diterpene Hydroxyethers from

Tobacco and Cigarette Smoke. J. ORG. CHEM. *29:* 16-21.

Saito Y, Takizawa H, Konishi S, Yoshida D, and Mizusaki S (1985), Identification of Cembratriene-4,6-diol as an Antitumor-Promoting Agent from Cigarette Smoke Condensate. CARCINOGENESIS *6:* 1189-1194.

Sakuma H, Kusama M, Munakata S, Ohsumi T, and Sugawara S (1983a), The Distribution of Cigarette Smoke Components between Mainstream and Sidestream Smoke. I. Acidic Components. BEITR. TABAKFORSCH. INTERNAT. *12:* 63-71.

Sakuma H, Kusama M, Yamaguchi K, Matsuki T, and Sugawara S (1983b), Sidestream (SS)/Mainstream (MS) Distribution Ratios of Cigarette Smoke Components. III. Medium and High Boiling Components. 37th TOB. CHEM. RES. CONF., Washington DC: Paper No. 41.

Sakuma H, Kusama M, Yamaguchi K, Matsuki T, and Sugawara S (1984a), The Distribution of Cigarette Smoke Components between Mainstream and Sidestream Smoke. II. Bases. BEITR. TABAKFORSCH. INTERNAT. *12:* 199-209.

Sakuma H, Kusama M, Yamaguchi K, and Sugawara S (1984b), The Distribution of Cigarette Smoke Components between Mainstream and Sidestream Smoke. III. Middle and High Boiling Components. BEITR. TABAKFORSCH. INTERNAT. *12:* 251-258.

Sall RD and Shear MJ (1940), Studies in Carcinogenesis. XII. Effect of the Basic Fraction of Creosote Oil on the Production of Tumors in Mice by Chemical Carcinogens. J. NATL. CANCER INST. *1:* 45-55.

Sasson IM, Coleman DT, LaVoie EJ, Hoffmann D, and Wynder EL (1985), Mutagens in Human Urine: Effects of Cigarette Smoking and Diet. MUTATION RES. *158:* 149-158.

Satterlee HS (1956), The Problem of Arsenic in American Cigarettes. NEW ENG. J. MED. *254:* 1149-1154.

Scanlan RA and Barbour JF (1991), *N*-Nitrosodimethylamine Content of U.S. and Canadian Beers. In O'Neill IK, Chen J, and Bartsch H (Editors), *Relevance to Human Cancer of* N-*Nitroso Compounds, Tobacco Smoke, and Mycotoxins*, IARC, Lyon, France. IARC SCI. PUBL. NO. 105: 242-243.

Scanlan RA, Barbour JF, Hotchkiss JW, and Libbey LM (1980), *N*-Nitrosodimethylamine in Beer. FOOD COSMET. TOXICOL. *18:* 27-29.

Scherer G, Ruppert T, Kossien I, Riedel K, and Adlkofer F (1993), Assessment of the Everyday Exposure to Environmental Tobacco Smoke (ETS) by Different Methods. 47th TOB. CHEM. RES. CONF., Gatlinburg TN, Paper No. 08.

Scherer G, Westphal H, Adlkofer F, and Sorsa M (1989), Biomonitoring of Exposure to Potentially Genotoxic Substances from Environmental Tobacco Smoke. ENVIRON. INTERNAT. *15:* 49-56.

Scherer G, Westphal H, Biber A, Hoepner I, and Adlkofer F (1987a), Urinary Mutagenicity after Controlled Exposure to Environmental Tobacco Smoke. TOXICOL. LETT. *35:* 135-140.

Scherer G, Westphal H, Hoepner I, and Adlkofer F (1987b), Biomonitoring of Exposure to Potentially Genotoxic Substances from Environmental Tobacco Smoke (ETS). In Seifert H, Esdorn H, Fischer M, Ruden H, and Wegner J (Editors), *Indoor Air '87*, Proc. 4th Internat. Conf. on Indoor Air Quality and Climate, West Berlin, Institute for Water, Soil and Air Hygiene, Vol. 2: 109-114.

Schlotzhauer WS and Schmeltz I (1969a), Role of the Hexane Soluble Fraction of Tobacco in the Formation of Aromatic Hydrocarbons Present in Tobacco Smoke. 23rd TOB. CHEM. RES. CONF., Philadelphia PA: Paper No. 28.

Schlotzhauer WS and Schmeltz I (1969b), Pyrogenesis of Aromatic Hydrocarbons Present in Cigarette Smoke. II. Pyrolytic Products of Some Constituents of the Hexane Soluble Fraction of Tobacco. BEITR. TABAKFORSCH. *5:* 5-8.

Schmeltz I and Hoffmann D (1977), Nitrogen-containing Compounds in Tobacco and Tobacco Smoke. CHEM. REV. *77:* 295-311.

Schmeltz I, Schlotzhauer WS, and Higman EB (1972), Characteristic Products from Pyrolysis of Nitrogenous Organic Substances. BEITR. TABAKFORSCH. *6:* 134-138.

Schmeltz I, Wenger A, Hoffmann D, and Tso TC (1979), Chemical Studies on Tobacco Smoke. 63. On the Fate of Nicotine during Pyrolysis and in a Burning Cigarette. J. AGR. FOOD CHEM. *27:* 602-608.

Schoenhard GL, Aksamit WW, Bible RK, Hansen LC, Hribar JD, Levon EF, Shubeck MP, and Wagner H (1978), In *Environmental Aspects of* N-*Nitroso Compounds*, IARC, Lyon, France, IARC SCI. PUBL. NO. 19: 78-85.

Searle CE (Editor) (1984), *Chemical Carcinogenesis, Second Edition*. American Chemical Society Monograph 182, American Chemical

Society, Washington DC.

Sebranek JG and Cassens RG (1973), Nitrosamines: A Review. J. MILK FOOD TECHNOL. *36:* 76-91.

Selikoff IJ, Hammond EC, and Lawther PJ (1969), Inhalation of Benzpyrene and Cancer in Man. ANN. MTG., AM. COLLEGE CHEST PHYS., Chicago IL (October 30).

Sen NP (1972), The Evidence for the Presence of *N*-Nitrosodimethylamine in Meat Products. FOOD COSMET. TOXICOL. *10:* 219.

Sen NP (1991), Recent Studies in Canada on the Occurrence and Formation of *N*-Nitroso Compounds in Foods and Food Contact Materials. In O'Neill IK, Chen J, and Bartsch H (Editors), *Relevance to Human Cancer of* N-*Nitroso Compounds, Tobacco Smoke, and Mycotoxins*, IARC, Lyon, France. IARC SCI. PUBL. NO. 105: 232-234.

Sen NP and Dalpe C (1972), A Simple Thin-Layer Chromatographic Technique for the Semi-Quantitative Determination of Volatile Nitrosamines in Alcoholic Beverages. ANALYST *97:* 216.

Sen NP, Donaldson B, Seaman S, Collins B, and Iyengar JR (1977), CAN. INST. FOOD SCI. TECHNOL. *10:* A13-A15.

Sen NP and Seaman S (1981a), Gas-Liquid Chromatographic-Thermal Energy Analyzer Determination of *N*-Nitrosodimethylamine in Beer at Low Parts per Billion Level. J. ASSOC. OFF. ANAL. CHEM. *64:* 933-938.

Sen NP and Seaman S (1984), On-Line Combination of High-Performance Liquid Chromatography and Total *N*-Nitroso Determination Apparatus for the Determination of *N*-Nitrosamides and Other *N*-Nitroso Compounds and Some Recent Data on the Levels of *N*-Nitrosoproline in Foods and Beverages. In O'Neill IK, von Borstel RC, Miller CT, Long J, and Bartsch H (Editors), N-*Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer.* IARC, Lyon, France, IARC SCI. PUBL. NO. 57: 137-143.

Sen NP, Seaman S, and Kushwaha S (1986), Prevention of Artifactual Formation of Nitrosamines during the Analysis of Baby Bottle Rubber Nipples. ANALYST *111:* 139-144.

Sen NP, Seaman S, and McPherson M (1980a), Nitrosamines in Alcoholic Beverages. J. FOOD SAFETY *2:* 13-18.

Sen NP, Seaman S, and Miles WF (1979), Volatile *N*-Nitrosamines in Various Cured Meat Products: Effect of Cooking and Recent Trends. J. AGR. FOOD CHEM. *27:* 1354-1360.

Sen NP, Smith DC, Schwinghamer L, and Howsam B (1970), CAN. INST. FOOD TECHNOL. *3:* 6.

Sen NP, Tessier I, and Seaman S (1983), Determination of *N*-Nitrosoproline and *N*-Nitrososarcosine in Malt and Beer. J. AGR. FOOD CHEM. *31:* 1033-1036.

Serfontein WJ and Hurter P (1964), Occurrence of Nitrosamines in the Smoke of South African Cigarettes. SOUTH AFRICAN MED. J. *38:* 617.

Serfontein WJ and Hurter P (1966), Nitrosamines as Environmental Carcinogens. II. Occurrence of Nitrosamines in Tobacco Smoke Condensate. CANCER RES. *26:* 575-579.

Severson RF, Schlotzhauer WS, Chortyk OT, Arrendale RF, and Snook ME (1979), Precursors of Polynuclear Aromatic Hydrocarbons in Tobacco Smoke. In Jones PW and Leber P (Editors), *3rd International Symposium on Carcinogenesis and Mutagenesis.* Ann Arbor Science, Ann Arbor MI: 277-298.

Shamberger RJ (1970), Relationship of Selenium to Cancer. Inhibitory Effect of Selenium on Carcinogenesis. J. NATL. CANCER INST. *44:* 931-936.

Shear MJ and Leiter J (1941), J. NATL. CANCER INST. *2:* 241-258.

Shimkin MB (1955), Pulmonary Tumors in Experimental Animals. ADV. CANCER RES. *3:* 223-267.

Shklar G (1982), Oral Mucosa Carcinogenesis in Hamsters. Inhibition by Vitamin E. J. NATL. CANCER INST. *68:* 791-797.

Shotadze DP (1953), Experimental Investigation of the Carcinogenic Influence of Tar. VOPROSY ONKOL. *6:* 90-93.

Shubik P and Hartwell JL (1957), *Survey of Compounds Which Have Been Tested for Carcinogenic Activity,* Suppl. 1, USPHS Publ. No. 149, Washington DC.

Shubik P and Hartwell JL (1969), *Survey of Compounds Which Have Been Tested for Carcinogenic Activity*, Suppl. 2, USPHS Publ. No. 149, Washington DC.

Skrabs R (1984), Workplace Studies in the Leather Industry: Health Aspects. LEDER *35:* 171-174.

Slack PT and Wainwright T (1981), Hordenine as the Precursor of NDMA in Malt. J. INST. BREW. *87:* 259-263.

Slaga TJ and Boutwell RK (1977), Inhibition of the Tumor-Initiating Ability of the Potent Carcinogen 7,12-Dimethylbenz[*a*]anthracene by the Weak Tumor Initiator 1,2,3,4-Dibenzanthracene. CANCER RES. *37:* 129-133.

Slaga TJ and Bracken WM (1977), The Effect of Antioxidants on Skin Tumor Initiation and Aryl Hydrocarbon Hydroxylase. CANCER RES. *37:* 1631-1635.

Slaga TJ and DiGiovanni J (1984), Inhibition of Chemical Carcinogenesis. In Searle CE (Editor), *Chemical Carcinogens, Second Edition*, **American Chemical Society Monograph 182**, American Chemical Society, Washington DC: 1279-1321.

Slaga TJ, Jecker L, Bracken WM, and Weeks CE (1979), The Effects of Weak or Non-carcinogenic Polycyclic Hydrocarbons on 7,12-Dimethylbenz[*a*]anthracene and Benzo[*a*]pyrene. CANCER LETT. *7:* 51-59.

Slaga TJ, Solanki VI, and Logani M (1983), Studies on the Mechanism of Action of Antitumor Promoting Agents: Suggestive Evidence for the Involvement of Free Radicals in Promotion. In Ngaard OF and Simic MG (Editors), *Radioprotectors and Anticarcinogens*, Academic Press, New York NY: 471-485.

Slaga TJ, Viaje A, Buty SG, and Bracken WM (1978), Dibenz[*a,c*]anthracene: A Potent Inhibitor of Skin-Tumor Initiation by 7,12-Dimethylbenz[*a*]anthracene. RES. COMM. CHEM. PATHOL. PHARMACOL. *19:* 477-483.

Snook ME (1978), Nitrogen Analogues of Polynuclear Aromatic Hydrocarbons in Tobacco Smoke. In Jones PW and Freudenthal RI (Editors), *Carcinogenesis: Polynuclear Aromatic Hydrocarbons. Vol. 3*, Raven Press, New York NY: 203-215.

Snook ME, Fortson PJ, and Chortyk OT (1981), Isolation and Identification of Aza-Arenes of Tobacco Smoke. BEITR. TABAKFORSCH. INTERNAT. *11:* 67-78.

Snook ME, Severson RF, Arrendale RF, Higman HC, and Chortyk OT (1977), The Identification of High Molecular Weight Polynuclear Aromatic Hydrocarbons in a Biologically Active Fraction of Cigarette Smoke Condensate. BEITR. TABAKFORSCH. INTERNAT. *9:* 79-101.

Snook ME, Severson RF, Arrendale RF, Higman HC, and Chortyk OT (1978), Multi-Alkylated Polynuclear Aromatic Hydrocarbons of Tobacco Smoke: Separation and Identification. BEITR. TABAKFORSCH. INTERNAT. *9:* 222-247.

Solenova LG, Krishosheeva LV, Smirnov GA, and Khesina AY (1990), *N*-Nitrosamines in the Air of Industries Producing Rubber Shoes and Industrial Rubber Goods. GIG. TR. PROF. ZABOL. *1990 (6):* 23-25.

Sorsa M, Einistoe P, Husgafvel-Pursiainen K, Jaerventaus H, Kivistoe H, Peltonen Y, Tuomi T, Valkonnen S, and Pelkonen O (1985), Passive and Active Exposure to Cigarette Smoke in a Smoking Experiment. J. TOXICOL. ENVIRON. HLTH. *16:* 523-534.

Sorsa M, Husgafvel-Pursiainen K, Jaerventaus H, Koskimies K, Salo H, and Vainio H (1989), Cytogenic Effects of Tobacco Smoke Exposure among Involuntary Smokers. MUTATION RES. *222:* 111-116.

Spiegelhalder B (1983a), Analysis of Malt and Malt Based Beverages: General Aspects. In Egan H, Preussmann R, O'Neill IK, Eisenbrand G, Spiegelhalder B, and Bartsch H (Editors), *Environmental Carcinogenesis: Selected Methods of Analysis, Vol. 6:* N-*Nitroso Compounds*, IARC, Lyon, France, IARC SCI. PUBL. NO. 45: 103-113.

Spiegelhalder B (1983b), Carcinogens in the Workroom Air in the Rubber Industry. SCAND. J. WORK ENV. HLTH. *9 (Suppl. 2):* 15-26.

Spiegelhalder B and Eisenbrand G (1982), In N-*Nitroso Compounds: Occurrence and Biologic Effects*, IARC, Lyon, France, IARC SCI. PUBL. NO. 41: 231-243.

Spiegelhalder B, Eisenbrand G, and Preussmann (1974), Influence of Dietary Nitrate on Nitrite Content of Human Saliva: Possible Relevance to *in vivo* Formation of *N*-Nitroso Compounds. FOOD COSMET. TOXICOL. *14:* 545-548.

Spiegelhalder B, Eisenbrand G, and Preussmann R (1979), Contamination of Beer with Trace Quantities of *N*-Nitrosodimethylamine. FOOD COSMET. TOXICOL. *17:* 29-31.

Spiegelhalder B, Eisenbrand G, and Preussmann R (1980), Volatile Nitrosamines in Food. ONCOLOGY *37:* 211-216.

Spiegelhalder B, Eisenbrand G, and Preussmann R (1983), Volatile *N*-Nitrosamines in Beer and Other Beverages by Direct Extraction Using a Kieselguhr Column. In Egan H, Preussmann R, O'Neill IK, Eisenbrand G, Spiegelhalder B, and Bartsch H (Editors), *Environmental Carcinogenesis: Selected Methods of Analysis, Vol. 6:* N-*Nitroso Compounds*, IARC, Lyon, France, IARC SCI. PUBL. NO. 45: 135-142.

Spiegelhalder B, Fischer S, and Preussmann R (1989a), Tobacco-Specific Nitrosamines in Mainstream Smoke of West German Cigarettes: Influence of Tar and Tobacco Type. In Maskens AP *et al.* (Editors), *Tobacco and Cancer. Perspectives in Preventive Research,* Excerpta Medica: 23-34.

Spiegelhalder B, Kubacki SJ, and Fischer S (1989b), A Method for the Determination of Tobacco-Specific Nitrosamines (TSNA), Nitrate and Nitrite in Tobacco Leaves and Processed Tobacco. BEITR. TABAKFORSCH. INTERNAT. *14:* 135-144.

Spiegelhalder B and Preussmann R (1984), Contamination of Toiletries and Cosmetic Products with Volatile and Nonvolatile *N*-Nitroso Carcinogens. J. CANCER RES. CLIN. ONCOL. *108:* 160-163.

Stedman RL (1968), The Chemical Composition of Tobacco and Tobacco Smoke. CHEM. REV. *68:* 153-207.

Stehlik G, Richter O, and Altmann H (1982), Concentration of Dimethylnitrosamine in the Air of Smoke-Filled Rooms. ECOTOXICOL. ENVIRONMENTAL SAFETY *6:* 495-500.

Steiner PE and Falk HL (1951), CANCER RES. *11:* 56-63.

Stephany RW and Schuller PL (1980), Daily Dietary Intakes of Nitrite, Nitrate and Volatile Nitrosamines in the Netherlands Using the Duplicate Sampling Technique. ONCOLOGY *37:* 203-210.

Stewart HL and Herrold KM (1962), A Critique of Experiments on Attempts to Induce Lung Cancer with Tobacco Derivatives. BULL. INST. INTERNAT. STAT., ACTES 33rd SESSION, Paris, France: *39:* 457-477.

Sugimura T, Kawachi T, Nagao M, Yohagi T, Seino Y, Okamoto T, Shudo K, Kosuge T, Tsuji K, Watabayashi K, Iitaka Y, and Ita A (1977), Mutagenic Principle(s) in Tryptophan and Phenylalanine Pyrolysis Products. PROC. JAPAN ACAD. *53B:* 58-61.

Szent-Gyorgyi A (1960), Removal of Polycyclic Aromatic Hydrocarbons from Cigarette Mainstream Smoke by Chloranil. Personal communication to R.J. Reynolds Tobacco Company.

Takeda K, Ukawa S, and Mochizuki M (1991), Inhibition by Fatty Acids of Direct Mutagenicity of *N*-Nitroso Compounds. In O'Neill IK, Chen J, and Bartsch H (Editors), *Relevance to Human Cancer of* N-*Nitroso Compounds, Tobacco Smoke, and Mycotoxins*, IARC, Lyon, France. IARC SCI. PUBL. NO. 105: 558-563.

Takenaka S, Oldiges H, Koenig H, Hochrainer D, and Oberdoerster G (1983), Carcinogenicity of Cadmium Chloride Aerosols in W Rats. J. NATL. CANCER INST. *70:* 367-373.

Teel R and Castonguay A (1992), Antimutagenic Effects of Polyphenolic Compounds. CANCER LETT. *66:* 107-113.

Ten Thije JH and Ressang A (1956), Lung Cancer in Dogs. NED. TIJDSCHR. GENEESK. *100:* 1207.

Terrell JH and Schmeltz I (1970), Alteration of Cigarette Smoke Composition. I. Influence of Certain Additives. TOB. SCI. *14:* 78-81.

Theiler R, Sato K, Aspelund T, and Miller A. (1984), Inhibition of *N*-Nitrosamine Formation in a Cured Ground Pork Belly Model System. J. FOOD SCI. *49:* 341-344.

Thomas JI *et al.* (1968/1969), *Survey of Compounds Which Have Been Tested for Carcinogenic Activity,* USPHS Publ. No. 149, Washington DC (1968/1969 Volume).

Thomas JI *et al.* (1970/71), *Survey of Compounds Which Have Been Tested for Carcinogenic Activity,* USPHS Publ. No. 149, Washington DC (1970/1971 Volume).

Thompson HC Jr, Billedeau SM, Miller BJ, Hansen EB Jr, Freeman JP, and Wind ML (1984), Determination of *N*-Nitrosamines and *N*-Nitrosamine Precursors in Rubber Nipples from Baby Pacifiers by Gas Chromatography Thermal Energy Analysis. J. TOXICOL. ENVIRON. HLTH. *13:* 615-632.

Toth B and Patil K (1983), Enhancing Effect of Vitamin E on Murine Intestinal Tumorigenesis by 1,2-Dimethylhydrazine Hydrochloride. J.

NATL. CANCER INST. *70:* 1107-1111.

Townsend DE (Editor) (1987), *Proceedings of the International Conference on the Physical and Chemical Processes Occurring in a Burning Cigarette.* R. J. Reynolds Tobacco Company, Winston-Salem NC.

Tricker AR, Ditrich C, and Preussmann R (1991), *N*-Nitroso Compounds in Cigarette Tobacco and Their Occurrence in Mainstream Tobacco Smoke. CARCINOGENESIS *12:* 257-262.

Tricker AR, Haubner R, Spiegelhalder B, and Preussmann R (1988), The Occurrence of Tobacco-Specific Nitrosamines in Oral Tobacco Products and Their Potential Formation Under Simulated Gastric Conditions. FOOD CHEM. TOXICOL. *26:* 861-865.

Tricker AR and Preussmann R (1988a), *N*-Nitroso Compounds and Their Precursors in the Human Environment. In Hill JM (Editor), *Nitrosamines: Toxicology and Microbiology*, VCH Publishers Inc., New York NY: 88-116.

Tricker AR and Preussmann R (1988b), The Occurrence of *N*-Nitroso Compounds in Zarda Tobacco. CANCER LETT. *42:* 113-118.

Tricker AR and Preussmann R (1989), Preformed Nitrosamines in Smokeless Tobacco. In Maskens AP *et al.* (Editors), *Tobacco and Cancer. Perspectives in Preventive Research.* Excerpta Medica: 35-47.

Tricker AR and Preussmann R (1991), Exposure to Nicotine Derived *N*-Nitrosamines from Smokeless Tobacco and Evidence Against Their Endogenous Formation. In Adlkofer F and Thurau K (Editors), *Effects of Nicotine on Biological Systems*, Birkhauser Verlag, Boston MA: 109-113.

Tricker AR, Scherer G, Adlkofer F, Pachinger A, and Klus H (1992), Exogenous and Endogenous Exposure to Tobacco-Specific Nitrosamines. 204th NATL. MTG., AM. CHEM. SOC., Washington DC: Paper No. 158.

Tricker AR, Spiegelhalder B, and Preussmann R (1989), Environmental Exposure to Preformed *N*-Nitroso Compounds. CANCER SURV. *8:* 251-272.

Tso TC, Sims JL, and Johnson DE (1975), Some Agronomic Factors Affecting *N*-Dimethylnitrosamine Content in Cigarette Smoke. BEITR. TABAKFORSCH. *8:* 34-38.

United States Food and Drug Administration (FDA) (1980), Dimethylnitrosamine in Malt Beverages: Availability of Guide. FED. REG. *45:* 39341-39342.

United States Public Health Service (USPHS) (1964), *Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service.* DHEW Publ. No. (PHS) 1103.

United States Public Health Service (USPHS) (1979), *Smoking and Health. A Report of the Surgeon General.* DHEW Publ. No. (PHS) 79-50066.

United States Public Health Service (USPHS) (1981), *The Health Consequences of Smoking. The Changing Cigarette. A Report of the Surgeon General.* DHHS Publ. No. (PHS) 81-50156.

United States Public Health Service (USPHS) (1982), *The Health Consequences of Smoking. Cancer. A Report of the Surgeon General.* DHHS Publ. No. (PHS) 82-50179.

United States Public Health Service (USPHS) (1987), *The Health Consequences of Involuntary Smoking. A Report of the Surgeon General, 1986.* DHHS Publ. No. (PHS) 87-8398.

United States Public Health Service (USPHS) (1989), *Reducing the Health Consequences of Smoking. 25 Years of Progress. A Report of the Surgeon General.* DHHS Publ. No. (PHS) 89-8411.

Van Duuren BL (1958), The Polynuclear Aromatic Hydrocarbons in Cigarette-Smoke Condensate. II. J. NATL. CANCER INST. *21:* 623-630.

Van Duuren BL, Bilbao JA, and Joseph CA (1960a), The Origin and Nature of the Nitrogen Heterocyclics in Cigarette Smoke Condensate. PROC. AM. CHEM. SOC. MTG.-IN-MINIATURE, New York NY.

Van Duuren BL, Bilbao JA, and Joseph CA (1960b), The Carcinogenic Nitrogen Heterocycles in Cigarette Smoke Condensate. J. NATL. CANCER INST. *25:* 53-61.

Van Duuren BL, Blazej T, Goldschmidt BM, Katz C, Melchionne S, and Sivak A (1971), Cocarcinogenesis Studies on Mouse Skin and Inhibition

of Tumor Induction. J. NATL. CANCER INST. *46:* 1039-1044.

Van Duuren BL, Katz C, and Goldschmidt BM (1973), Brief Communication: Cocarcinogenic Agents in Tobacco Carcinogenesis. J. NATL. CANCER INST. *51:* 703-705.

Vecchio AJ, Ax JH (1986), *N*-Nitrosamine Ingestion from Consumer-Cooked Bacon. J. FOOD SCI. *51:* 754.

Viaje A, Siege TJ, Wigler M, and Weinstein IB (1977), Effects of Anti-inflammatory Agents in Mouse Skin Tumor Promotion, Epidermal DNA Synthesis, Phorbol Ester-Induced Cellular Proliferation, and Production of Plasminogen Activator. CANCER RES. *37:* 1530-1536.

Vilcins G and Lephardt JO (1974a), Aging Process of Cigarette Smoke: Formation of Methyl Nitrite. 28th TOB. CHEM. RES. CONF., Raleigh NC: Paper No. 52.

Vilcins G and Lephardt JO (1974b), Aging Process of Cigarette Smoke: Formation of Methyl Nitrite. CHEM. AND IND. (London) 974-975.

Waddell W, and Marlowe C (1983), Inhibition by Alcohols of the Localization of Radioactive Nitrosonornicotine in Sites of Tumor Formation. SCIENCE *221:* 51-52.

Wakeham H (1971), Recent Trends in Tobacco and Tobacco Smoke Research. Symposium on the Composition of Tobacco and Tobacco Smoke. AM. CHEM. SOC. MTG., Washington DC.

Wakeham H (1972), Recent Trends in Tobacco and Tobacco Smoke Research. In Schmeltz I (Editor), *The Chemistry of Tobacco and Tobacco Smoke*, Plenum Press, New York NY: 1-20.

Wakeham H (1976a), Sales Weighted Average Tar and Nicotine Deliveries of U.S. Cigarettes from 1957 to the Present. In Wynder EL and Hecht SS (Editors), *Lung Cancer*, UICC TECH. RPT. SERIES *25:* 151-152.

Wakeham HRR (1976b), Environmental Carbon Monoxide from Cigarette Smoking. PROC. 6th INTERNAT. TOB. SCI. CONG., Tokyo, Japan, 1976: 93-101.

Wakeham HRR (1977), Environmental Carbon Monoxide from Cigarette Smoking: A Critique. PREV. MED. *6:* 526-534.

Waldman JM, Lioy PJ, Greenberg A, and Butler JP (1991), Analysis of Human Exposure to Benzo(a)pyrene Via Inhalation and Food Ingestion in the Total Human Exposure Study (THEES). J. EXPOSURE ANAL. ENVIRON. EPIDEMIOL. *1:* 193-225.

Walker EA, Castegnaro M, Garren L, Toussaint G, and Kowalski B (1979), Intake of Volatile Nitrosamines from Consumption of Alcohols. J. NATL. CANCER INST. *63:* 947-951.

Warshawsky D, Barkley W, and Bingham E (1993), Factors Affecting Carcinogenic Potential of Mixtures. FUND. APPL. TOXICOL. *20:* 376-382.

Wasserman AE, Fiddler W, Doerr RC, Osman SF, and Dooley CJ (1972), FOOD COSMET. TOXICOL. *10:* 681.

Wattenberg LW (1975), Inhibition of Dimethylhydrazine-Induced Neoplasia of the Large Intestine by Disulfiram. J. NATL. CANCER INST. *54:* 1005-1006.

Wattenberg LW (1981), Inhibitors of Chemical Carcinogens. In Burchenal JH (Editor), *Cancer: Achievements, Challenges and Prospects for the 1980's*, Grune and Stratton, New York NY: 517-539.

Wattenberg LW (1985), Chemoprevention of Cancer. CANCER RES. *45:* 1-8.

Wattenberg LW and Coccia JB (1991), Inhibition of 4-Methylnitrosamino-1-(3-pyridyl)-1-butanone Carcinogenesis in Mice by *D*-Limonene and Citrus Fruit Oils. CARCINOGENESIS *12:* 115-117.

Wattenberg LW, Coccia JB, and Lam LKT (1980), Inhibitory Effects of Phenolic Compounds on Benzo[*a*]pyrene-Induced Neoplasia. CANCER RES. *40:* 2820-2823.

Wattenberg LW and Fiala ES (1978), Inhibition of 1,2-Dimethylhydrazine-Induced Neoplasia of the Large Intestine in Female CF1 Mice by Carbon Disulfide. J. NATL. CANCER INST. *60:* 1515-1517.

Wattenberg LW, Lam LKT, and Fladmoe AV (1979), Inhibition of Chemical Carcinogen-Induced Neoplasia by Coumarins and Angelica Lactone. CANCER RES. *39:* 1651-1654.

Webb KS and Gough TA (1980), ONCOLOGY *37:* 195-198.

Weber KH (1976), Recent Changes in Tobacco Products and Their Acceptance by Consumers. PROC. 6th INTERNAT. TOB. SCI. CONG., Tokyo, Japan, 1976: 47-63.

Weerapradist W and Shklar G (1982), Vitamin E Inhibition of Hamster Buccal Pouch Carcinogenesis. ORAL SURG. *54:* 304-312.

Wehner AP, Dagle GE, Milliman EM, Phelps DW, Carr DB, Decker JR, and Filipy RE (1981), Inhalation Bioassay of Cigarette Smoke in Rats. TOXICOL. APPL. PHARMACOL. *61:* 1-17.

Weiss ST, Tager IB, Schenker M, and Speizer FE (1983), State of the Art: The Health Effects of Involuntary Smoking. AM. REV. RESP. DIS. *128*: 933-942.

Weller RW (1954), Life Time Cigarette Smoke Exposure in a Colony of C57 Black Mice. AM. MED. ASSOC. MTG. San Francisco CA.

Wilbourn J, Haroun L, Heseltine E, Kaldor J, Partensky C, and Vainio H (1966), Response of Experimental Animals to Human Carcinogens: An Analysis Based upon the IARC Monographs Programme. CARCINOGENESIS *7:* 1853-1863.

Williams R, Sparacino C, Petersen B, Bumgarner J, Jungers RH, and Lewtas J (1986), Comparative Characterization of Organic Emissions from Diesel Particles, Coke Oven Mains, Roofing Tar Vapors and Cigarette Smoke Condensate. INTERNAT. J. ENVIRON. ANAL. CHEM. *26:* 27-49.

Wolf D (1989), *N*-Nitrosamines at Workplaces. STAUB. REINHALT LUFT *49:* 183-186.

Wolf D, Blome H, and Schuetz A (1984), Problems in the Measurement and Estimation of Carcinogenic Working Materials of Group I in Industrial Workplace Atmospheres Exemplified by *N*-Nitrosamines. STAUB. REINHALT LUFT *44:* 33-37.

Wolff IA and Wasserman AE (1972), Nitrates, Nitrites, and Nitrosamines. SCIENCE *177:* 15-19.

Wright GF (1957a), Studies with Tobacco Smoke Condensate. In *Proc. 3rd Natl. Cancer Conf., June, 1956,* JB Lippincott Company: 479-484.

Wright GF (1957b), Personal communication to A. Rodgman (July 22).

Wynder EL (1956), Human and Experimental Relation of Tobacco and Cancer. TOB. SYMP., LONG ISLAND SUBSECTION, AM. CHEM. SOC.

Wynder EL (1959), Laboratory Contributions to the Tobacco-Cancer Problem. BRIT. MED. J. *1959 (i):* 317-322.

Wynder EL (1961), Laboratory Contributions to the Tobacco-Cancer Problem. ACTA MED. SCAND. *170 (Suppl. 369):* 63-101.

Wynder EL (1964), Studies in Tobacco Carcinogenesis. PROC. AM. ASSOC. CANCER RES. *5 (1):* 70.

Wynder EL, Fritz L, and Furth N (1957), Effect of Concentration of Benzopyrene in Skin Carcinogenesis. J. NATL. CANCER INST. *19:* 361-370.

Wynder EL, Goodman DA, and Hoffmann D (1965a), Ciliatoxic Components in Cigarette Smoke. II. Carboxylic Acids and Aldehydes. CANCER *18:* 505-509.

Wynder EL, Goodman DA, and Hoffmann D (1965b), Ciliatoxic Components in Cigarette Smoke. III. *in vitro* Comparison of Different Smoke Components. CANCER *18:* 1652-1658.

Wynder EL, Graham EA, and Croninger AB (1953a), Study on the Experimental Production of Cancer with Tobacco Tar. PROC. AM. ASSOC. CANCER RES. *1:* 62-63.

Wynder EL, Graham EA, and Croninger AB (1953b), Experimental Production of Carcinoma with Cigarette Tar. CANCER RES. *13:* 855-864.

Wynder EL, Graham EA, and Croninger AB (1955), Experimental Production of Carcinoma with Cigarette Tar. II. Tests with Different Mouse Strains. CANCER RES. *15:* 445-448.

Wynder EL and Hecht SS (Editors) (1976), Lung Cancer. UICC TECH. REPT. SERIES *25:* 138.

Wynder EL and Hoffmann D (1959a), The Role of Higher Polycyclic Hydrocarbons in Tobacco Carcinogenesis.

PROC. AM. ASSOC. CANCER RES. *3 (1):* 74.

Wynder EL and Hoffmann D (1959b), A Study of Tobacco Carcinogenesis. VII. The Role of Higher Polycyclic Hydrocarbons. CANCER *12:* 1079-1086.

Wynder EL and Hoffmann D (1960), Studies in Tobacco Carcinogenesis. PROC. AM. ASSOC. CANCER RES. *3 (2):* 164.

Wynder EL and Hoffmann D (1961a), Biological and Chemical Studies of Tobacco Smoke Condensate. PROC. AM. ASSOC. CANCER RES. *3 (3):* 280.

Wynder EL and Hoffmann D (1961b), Present Status of Laboratory Studies on Tobacco Carcinogenesis. ACTA PATH. MICROBIOL. SCAND. *52:* 119-132.

Wynder EL and Hoffmann D (1962a), A Study of Air Pollution Carcinogenesis. III. Carcinogenic Activity of Gasoline Engine Exhaust Condensate. CANCER *15:* 103-108.

Wynder EL and Hoffmann D (1962b), Studies with the Gaseous and Particulate Phase of Tobacco Smoke. PROC. AM. ASSOC. CANCER RES. *3 (4):* 373.

Wynder EL and Hoffmann D (1963a), A Method for Determining Ciliastatic Components in Cigarette Smoke. CANCER *16:* 1222-1225.

Wynder EL and Hoffmann D (1963b), Ein experimenteller Beitrag zur Tabakrauchkanzerogenese. DEUT. MED. WCHNSCHR. *88:* 623-628.

Wynder EL and Hoffmann D (1963c), Filtration of Phenols from Cigarette Smoke. J. NATL. CANCER INST. *30:* 67-84.

Wynder EL and Hoffmann D (1963d), Bioassays on the Carcinogenicity of Tobacco Smoke Condensate and Air Pollutants. PROC. AM. ASSOC. CANCER RES. *4 (1):* 73.

Wynder EL and Hoffmann D (1964), Experimental Tobacco Carcinogenesis. ADV. CANCER RES. *8:* 249-453.

Wynder EL and Hoffmann D (1965), Reduction of Tumorigenicity of Cigarette Smoke. An Experimental Approach. J. AM. MED. ASSOC. *192:* 88-94.

Wynder EL and Hoffmann D (1967), *Tobacco and Tobacco Smoke: Studies in Experimental Carcinogenesis.* Academic Press, New York NY.

Wynder EL and Hoffmann D (1968), Experimental Tobacco Carcinogenesis. SCIENCE *162:* 862-871.

Wynder EL, Kopf P, and Ziegler H (1957a), Dose Response with Cigarette Tar. PROC. AM. ASSOC. CANCER RES. *2 (3):* 261.

Wynder EL, Kopf P, and Ziegler H (1957b), A Study of Tobacco Carcinogenesis. II. Dose-Response Studies. CANCER *10:* 1193-1200.

Wynder EL, Lupberger A, and Grener C (1956), Experimental Production of Cancer with Cigarette Tar: Strain Differences. BRIT. J. CANCER *10:* 507-509.

Wynder EL and Wright GF (1955), Fractionation of Cigarette Tar. PROC. AM. ASSOC. CANCER RES. *2 (1):* 55.

Wynder EL and Wright GF (1957), A Study of Tobacco Carcinogenesis. I. The Primary Fractions. CANCER *10:* 255-271.

Wynder EL, Wright GF, and Lam J (1958a), A Study of Tobacco Carcinogenesis. V. The Role of Pyrolysis. PROC. AM. ASSOC. CANCER RES. *2 (4):* 357-358.

Wynder EL, Wright GF, and Lam J (1958b), A Study of Tobacco Carcinogenesis. V. The Role of Pyrolysis. CANCER *11:* 1140-1148.

Wynder EL, Wright GF, and Lam J (1959), A Study of Tobacco Carcinogenesis. VI. The Role of Precursors. CANCER *12:* 1073-1078.

Yamagiwa K (1965), *Collected Papers on Artificial Production of Cancer.* Maruzen Company Ltd., Tokyo, Japan.

Yamagiwa K and Ichikawa K (1915), Experimentelle Studie über die Pathogenese der Epithelialgeschwülste. TOKYO IGAKKAI ZASSI *15:* 295-344.

Yamagiwa K and Ichikawa (1918), J. CANCER RES. *3:* 1.

Yamamoto T, Tsuji K, Kosuge T, Okamoto T, Shudo K, Takeda K, Iitaka Y, Yamaguchi K, Seino Y, Yahagi T, Nagao M, and Sugimura T (1978), Isolation and Structure Determination of Mutagenic Substances in *L*-Glutamic Acid Pyrolysate. PROC. JAPAN ACAD. *54B:* 248-250.

Yamasaki E and Ames BN (1977), Concentration of Mutagens from Urine by Absorption with Polar Resin XAD2: Cigarette Smokers Have Mutagenic Urine. PROC. NATL. ACAD. SCI. *75:* 3555-3559.

Yamashita M, Wakabashi K, Nagao M, Sato S, and Kinea N (1985), Amounts of Heterocyclic Amines in the Basic Fraction of Cigarette Smoke Condensates. ENVIRON. MUTAGEN SOC. JAPAN MTG., Akita, Japan. See Abstr. in MUTATION RES. *164:* 286 (1986).

Yamashita M, Wakabashi K, Nagao M, Sato S, Yamaizumi Ž, Takahashi M, Kinea N, Tomita I, and Sugimura T (1986), Detection of 3-Amino-3-methylimidazo[4,5-*f*]quinoline in Cigarette Smoke Condensate. GANN *77:* 419-422.

Yasukawa K, Takido M, Matsumoto T, Takeuchi M, and Nakagawa S (1991), Sterol and Triterpene Derivatives from Plants Inhibit the Effects of a Tumor Promoter and Sitosterol and Betulic Acid Inhibit Tumor Formation in Mouse Skin Two-Stage Carcinogenesis. ONCOLOGY *48:* 72-76.

Zerban H, Preussmann R, and Bannasch P (1988), Dose-Time Relationship of the Development of Preneoplastic Liver Lesions Induced in Rats with Low Doses of *N*-Nitrosodiethanolamine. CARCINOGENESIS *9:* 607-610.

Zweig G, Selim S, Hummel R, Mitelman A, Wright DP, Law C, and Regezman E (1982), In Bartsch H, O'Neill IK, Castegnaro M, and Okada (Editors), N-*Nitroso Compounds: Occurrence and Biologic Effects*, IARC, Lyon, France, IARC SCI. PUBL. NO. 41: 554-564.